(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number
WO 02/09706 A1

(51) International Patent Classification[7]: A61K 31/427, 31/433, 31/4709, 31/4436, 31/5377, C07D 277/14, 417/02

(21) International Application Number: PCT/US01/23395

(22) International Filing Date: 24 July 2001 (24.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/629,248 27 July 2000 (27.07.2000) US

(71) Applicant: AFFYMAX RESEARCH INSTITUTE [US/US]; 4001 Miranda avenue, Palo Alto, CA 94304 (US).

(72) Inventors: **SCHEUERMAN, Randall, A.**; 963 Sunlite Drive, Santa Clara, CA 95050 (US). **YANOFSKY, Stephen, D.**; 3781 Nathan Way, Palo Alto, CA 94303 (US). **HOLMES, Christopher, P.**; 13633 Westover Drive, Saratoga, CA 95070 (US). **MACLEAN, Derek**; 1593 Lloyd Way, Mountain View, CA 94040 (US). **RUHLAND, Beatrice**; 481 Casita Way, Los Altos, CA 94024 (US). **BARRETT, Ronald, W.**; 12900 Arroyo de Arguello, Saratoga, CA 95070 (US). **WROBEL, Jay, E.**; 15 Rosetree Lane, Lawrenceville, NJ 08648 (US). **KAO, Wenling**; 1742 Jenning Way, Paoli, PA 19301 (US). **GOPALSAMY, Ariamala**; 1106 Devon Court, Mahwah, NJ 07430 (US). **SUM, Fuk-wah**; 16 Chamberlain Court, Pomona City, NY 10970 (US). **HU, Baihua**; 1 S. Lexow Avenue, Nanuet, NY 10954 (US). **ROGERS, John, F.**; 226 Lee Circle, Bryn Mawr, PA 19010 (US). **JETTER, James, W.**; 3030 Brambling Lane, Norristown, PA 19403 (US).

(74) Agents: **JEWETT, Stephen** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, Eigth Floor, San Francisco, CA 94111-3834 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/09706 A1

(54) Title: AGONISTS OF FOLLICLE STIMULATING HORMONE ACTIVITY

(57) Abstract: In one aspect, the present invention provides novel compounds. In addition, the invention provides a FSH receptor agonist, wherein the agonist binds to a FSH receptor having a FSH binding site and, wherein the agonist is noncompetitve with FSH for the FSH binding site. In another aspect, the invention provides methods of using the compounds of the present invention for diverse pharmaceutical applications including, for example, CNS antiischemic agents, agents with antipsychotic or other psychoactive properties, antimicrobial agents and mammalian fertility regulating agent.

AGONISTS OF FOLLICLE STIMULATING HORMONE ACTIVITY

FIELD OF THE INVENTION

This invention relates broadly to novel thiazolidinones. More specifically, the invention relates to thiazolidinones which modulate Follicle Stimulating Hormone (FSH) activity.

BACKGROUND OF THE INVENTION

Approximately 400,000 germ cells are stored in the ovaries of the human female at the time of puberty. No further germ cells are made. Beginning at the time of puberty and ending at menopause, there are approximately 400 ovulatory menstrual cycles which consume essentially all of the germ cells in the human ovary. About 1,000 germ cells are consumed in each menstrual period. However, in any one menstrual cycle, only one germ cell, developed in what becomes the dominant follicle, is ovulated and available for pregnancy.

Although the details are not accurately known, the mechanism by which a single egg is selected each month to become the dominant egg is dependent upon a complex interaction between one or more hormones from the ovary, hypothalamus and the pituitary. Three glycoprotein hormones (luteinizing hormone (LH), follicle stimulating hormone (FSH) and chorionic gonadotropin (hCG)) act on the ovary to stimulate steroid synthesis and secretion. LH and FSH are secreted by the pituitary and together play a central role in regulating the menstrual cycle and ovulation. hCG is secreted by the developing placenta from the early stages of pregnancy and its role is to maintain steroid secretion by the corpus luteum, which is necessary to prevent ovulation during pregnancy.

In the normal cycle, there is a mid-cycle surge in LH concentration which is followed by ovulation. An elevated estrogen level, which is brought about by the endogenous secretion of LH and FSH, is required for the LH surge to occur. The estrogen mediates a positive feedback mechanism which results in the increased LH secretion.

For more than twenty years, it has been possible to induce ovulation and menstruation, and sometimes pregnancy, in patients whose ovulatory mechanism is deranged so that normal cyclic ovulation and menstruation does not occur, by the administration of suitable amounts of a 1:1 mixture of FSH and LH known as human menopausal gonadotropin (hMG). In the field of *in vitro* fertilization, exogenous

hormonal stimulation is employed by administering hMG. Women treated with hMG, however, often fail to demonstrate a timely LH surge despite serum estradiol levels sufficient to elicit positive feedback of LH secretion.

It is well established that the appropriate application of mixed exogenous gonadotrophins is efficacious for ovulation induction or for multiple egg retrieval during *in vitro* fertilization therapy in women. However, ovarian stimulation through exogenous gonadotrophins for *in vivo* and *in vitro* fertilization therapy is notoriously difficult to manage and the lack of uniform success with conventional hMG medications is widely appreciated. Individual response to hMG varies markedly, thereby complicating patient management even when the most flexible (individualized) protocols are used.

Attempts have been made to vary therapeutic hormone regimens in order to provide improved methods of inducing ovulation which increase the likelihood of more uniform follicular maturation or ovulation. One such attempt involves the induction of follicular maturation or ovulation by the administration of FSH in the absence of exogenous LH. Hodgen, U.S. Patent No. 4,854,077. To produce FSH which is uncontaminated by LH, post-menopausal urinary gonadotropin has been purified using immunoaffinity chromatography and reverse-phase HPLC. Arpaia, *et al.*, U.S. Patent No. 5,128,453. Additional advances in this area have been realized by the use of hMG preparations which contain a markedly increased ratio of FSH to LH. Jones, Jr., *et al.*, U.S. Patent No. 4,725,579.

Other hormone preparations which have been used to treat infertility include somatotrophin releasing factor (GRF) either alone or in combination with FSH. Fabbri, *et al.*, U.S. Patent No. 5,017,557. Studies carried out in normal subjects during the menstrual cycle have demonstrated that intravenous administration of GRF produces an increase in serum levels of somatomedin C, but not of LH or FSH. Evans, *et al.* "Effects of human pancreatic growth hormone releasing factor 40 on serum growth hormone, prolactin, luteinizing hormone, follicle stimulating hormone and somatomedin C concentrations in normal women throughout the menstrual cycle." *J. Clin. Endoc. Metab.* **59**:1006 (1984). Two synthetic compounds, buserelin and triptorelin, have been used as gonadotrophin-releasing hormone agonists. *See*, for example, Out, *et al.*, "A prospective, randomized, assessor-blind, multicentre study comparing recombinant FSH (Puregon) either given intramuscularly or subcutaneously in subjects undergoing IVF." *Hum.*

Reprod. **10** (Abstract Book 1):6 (1995), and Hedon, *et al.*, "Efficacy and safety of recombinant FSH (Puregon) in infertile women pituitary-suppressed with triptorelin undergoing *in vitro* fertilization: a prospective, randomized, assessor-blind, multicentre trial." *Hum. Reprod.* **10**: 3102-3106 (1995). Currently, there are no small molecule FSH receptor agonists available for clinical use.

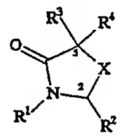
Thiazolidinones are a class of small molecule organic compounds which have found limited pharmaceutical use. For example, thiazolidinones have been found to have central nervous system activity. *See*, for example, Tripathi, *et al.*, "Thiazolidinone congeners as central nervous system active agents." *Arzneimittelforschung* **43**:632-5 (1993). CNS activities which have been identified include, for example, antipsychotic properties. *See*, Mutlib, *et al.*, "Metabolism of an atypical antipsychotic agent, 3-[4-[4-(6-fluorobenzo[b]thien-3-yl)-1-piperazinyl]butyl]-2,5,5-trimethyl-4-thiazolidinone (HP236)." *Drug Metab. Dispos.* **24**:1139-50 (1996). Other thiazolidinones have been found to be CNS antiischemic agents. *See*, Ruterbories, *et al.*, "Pharmacokinetics of a novel butylated hydroxytoluene-thiazolidinone CNS antiischemic agent LY256548 in rats, mice, dogs and monkeys." *Drug Metab. Dispos.* **18**:674-9 (1990). Thiazolidinones have also been used as antimicrobial agents. *See*, for example, Ley, *et al.*, "Inhibition of multiplication of Mycobacterium leprae by several antithyroid drugs." *Am. Rev. Respir. Dis.* **111**:651-5 (1975).

The synthesis of novel thiazolidinones offers the promise for discovering new pharmaceutical agents with applications in areas as diverse as, for example, antimicrobial therapy and the treatment of strokes with CNS antiischemic agents. Of particular interest is the use of novel thiazolidinones as regulators of mammalian fertility.

Although the recent introduction of recombinant FSH has eliminated many of the difficulties associated with the use of gonadotrophins of urinary origin (*e.g.*, cumbersome collection of urine, contamination of FSH by LH and low specific activity), there remains still a need for new fertility-regulating agents which are useful for both *in vivo* and *in vitro* applications. A class of small molecule FSH receptor agonist compounds which are inexpensive to prepare, easily purified, easily administered and which exhibit a broad range of activities would represent a significant advance in the field of human fertility medicine. Quite surprisingly, the present invention provides such small molecule thiazolidinone FSH receptor agonists.

SUMMARY OF THE INVENTION

The present invention provides a class of novel thiazolidinones possessing a range of pharmaceutical applications and activities. Thus, in one aspect, the present invention provides novel thiazolidinones having the formula:



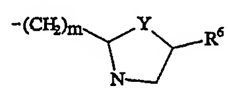
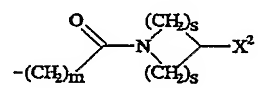
(I)

wherein,

R^1 is a member selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocyclic and substituted heterocylic groups;

R^2 is a member selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocylic groups;

R^3 and R^4 are independently members selected from the group including hydrogen, alkyl, $-(CH_2)_mCONR^5R^6$, $-(CH_2)_mOCONR^5R^6$, $-(CH_2)_mCH_2Y^2R^6$, $-(CH_2)_mCH{=}CHR^6$,

 , 

and $-(CH_2)_mCH_2NR^5CO(Y^3)_nR^6$;

R^5 and R^6 are independently members selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, arylalkyl, substituted arylalkyl, heterocyclicalkyl and substituted heterocyclicalkyl groups;

X is a member selected from the group consisting of S, S=O, and O=S=O;

Y is a member selected from the group consisting of O, S, and NH;

Y^2 is a member selected from the group consisting of CH_2, O, S, and NR^5;

Y^3 is a member selected from the group consisting of O and NR^7;

R^7 is a member selected from the group consisting of hydrogen and lower alkyl;

X^2 is a member selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, phenyl, substituted phenyl, heterocyclic,

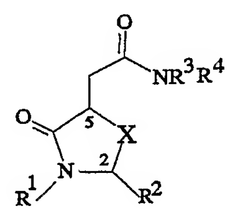
substituted heterocyclic, arylalkyl, substituted arylalkyl, heterocyclicalkyl and substituted heterocyclicalkyl groups;

m is an integer from 0 to 3;

n is 0 or 1; and

s is 1 or 2.

In a second aspect, the present invention provides novel thiazolidinones having the structure:



(III)

wherein,

R^1 is a member selected from the group consisting of aryl, substituted aryl, arylalkyl and substituted arylalkyl groups;

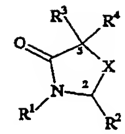
R^2 is a member selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic groups;

R^3 and R^4 are independently members selected from the group consisting of hydrogen, alkyl, substituted alkyl, arylalkyl, substituted arylalkyl, heterocyclic and substituted heterocyclic groups; and

X is a member selected from the group consisting of S, S=O, and O=S=O.

In another aspect, the invention provides a class of FSH receptor agonists, wherein the receptor agonists are noncompetitive with FSH for the receptor FSH binding site.

In yet another aspect, the invention provides a class of compounds that modulate FSH hormone activity, the compounds having: (a) a molecular weight of from about 50 daltons to about 1000 daltons; and (b) an FSH agonist activity corresponding to an EC_{50} standard of no more than 50 μM, preferably no more than 2 μM; wherein the agonist activity of this class of compounds to the FSH receptor is competitively inhibited by a compound having the formula:



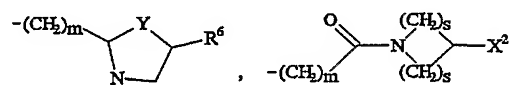
(I)

wherein,

R^1 is a member selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocyclic and substituted heterocylic groups;

R^2 is a member selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocylic groups;

R^3 and R^4 are independently members selected from the group including hydrogen, alkyl, $-(CH_2)_mCONR^5R^6$, $-(CH_2)_mOCONR^5R^6$, $-(CH_2)_mCH_2Y^2R^6$, $-(CH_2)_mCH{=}CHR^6$, $-(CH_2)_mCH_2NR^5CO(Y^3)_nR^6$,



R^5 and R^6 are independently members selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, arylalkyl, substituted arylalkyl, heterocyclicalkyl and substituted heterocyclicalkyl groups;

X is a member selected from the group consisting of S, S=O, and O=S=O;

Y is a member selected from the group consisting of O, S, and NH;

Y^2 is a member selected from the group consisting of CH_2, O, S, and NR^5;

Y^3 is a member selected from the group consisting of O and NR^6R^7;

R^7 is a member selected from the group consisting of hydrogen and lower alkyl;

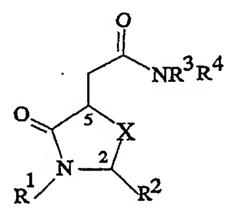
X^2 is a member selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, phenyl, substituted phenyl, heterocyclic, substituted heterocyclic, arylalkyl, substituted arylalkyl, heterocyclicalkyl and substituted heterocyclicalkyl groups;

m is an integer from 0 to 3;

n is 0 or 1; and

s is 1 or 2.

In yet a further aspect, the invention provides a class of compounds that modulate FSH hormone activity, the compounds having: (a) a molecular weight of from about 200 daltons to about 1000 daltons; and (b) an FSH agonist activity corresponding to an EC_{50} standard of no more than 50 μM, preferably no more than 2 μM; wherein the agonist activity of this class of compounds to the FSH receptor is competitively inhibited by a compound having the formula:



(III)

wherein: R^1 is a member selected from the group consisting of aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocyclic and substituted heterocyclic groups; R^2 is a member selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic groups; R^3 and R^4 are independently members selected from the group consisting of hydrogen, alkyl, substituted alkyl, arylalkyl, substituted arylalkyl, heterocyclic and substituted heterocyclic groups; and X is a member selected from the group consisting of S, S=O, and O=S=O.

In a preferred embodiment, this class of compounds has a molecular weight of about 300 daltons to about 800 daltons. In another preferred embodiment, this class of compounds has an FSH receptor agonist activity, as expressed by an EC_{50} standard, of no more than 1 μM and, more preferably, of no more than 500 nM.

In still another aspect, the invention provides methods of using the compounds, *i.e.,* thiazolidinones, for diverse pharmaceutical applications including, for example, CNS antiischemic agents, agents with antipsychotic or other psychoactive properties, antimicrobial agents and mammalian fertility regulating agents. When used as mammalian fertility regulating agents, the thiazolidinones are preferably agonists of the FSH receptor.

As such, in another aspect, the present invention provides pharmaceutical compositions which contain one or more of the compounds of the invention in conjunction with pharmaceutically acceptable excipients, carriers, diluents, *etc.* The pharmaceutical

compositions can also contain agents which are themselves pharmacologically active and which serve to enhance, supplement, decrease or otherwise regulate the pharmacological effect of the pharmaceutical compositions.

Other features, objects and advantages of the invention and its preferred embodiments will become apparent from the detailed description which follows.

DETAILED DESCRIPTION OF THE INVENTION

A. Abbreviations and Definitions

HATU, [O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate]; DIEA, diisopropylethylamine; FMOC, fluorenylmethoxycarbonyl; DECP, diethyl cyanophosphonate; DCM, dichloromethane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; CHO, chinese hamster ovary; RBF, round-bottomed flask.

The term "independently selected" is used herein to indicate that the R groups, *e.g.*, R^1, R^2, R^4 and R^5, can be identical or different (e.g., R^1, R^2 and R^3 may all be substituted alkyls or R^1 and R^2 may be a substituted alkyl and R^3 may be an aryl, etc.).

A named R group will generally have the structure which is recognized in the art as corresponding to R groups having that name. For the purposes of illustration, representative R groups as enumerated above are defined herein. These definitions are intended to supplement and illustrate, not preclude, the definitions known to those of skill in the art.

The term "alkyl" is used herein to refer to a branched or unbranched, saturated or unsaturated, monovalent hydrocarbon radical having from 1-12 carbons and preferably, from 1-6 carbons. When the alkyl group has from 1-6 carbons, it is referred to as a "lower alkyl." Suitable alkyl radicals include, for example, methyl, ethyl, n-propyl, i-propyl, 2-propenyl (or allyl), n-butyl, t-butyl (or 2-methylpropyl), *etc.*

"Substituted alkyl" refers to alkyl as just described including one or more functional groups such as lower alkyl, aryl, acyl, halogen, (*i.e.*, alkylhalos, *e.g.*, CF_3), hydroxy, nitro, cyano, amino, alkoxy, alkylamino, acylamino, acyloxy, aryloxy, arloxyalkyl, mercapto, carboxylic acid, carboxylic acid derivatives, sulfonic acids, sulfonic acid derivatives, both saturated and unsaturated cyclic hydrocarbons, heterocycles and the like. These groups may be attached to any which are fused to the arom

heterocycles and the like. These groups may be attached to any carbon of the alkyl moiety.

The term "aryl" is used herein to refer to an aromatic substituent having a single aromatic ring or multiple aromatic rings which are fused together, linked covalently, or linked to a common group such as a methylene or ethylene moiety. The common linking group may also be a carbonyl as in benzophenone. The aromatic ring(s) may include phenyl, naphthyl, biphenyl, diphenylmethyl and benzophenone among others.

"Substituted aryl" refers to aryl as just described including one or more functional groups such as lower alkyl, acyl, halogen, alkylhalos (*e.g.*, CF_3), hydroxy, nitro, cyano, amino, alkoxy, alkylamino, acylamino, acyloxy, mercapto, carboxylic acid amide, sulfonic acid amide and both saturated and unsaturated cyclic hydrocarbons which are fused to the aromatic ring(s), linked covalently or linked to a common group such as a methylene or ethylene moiety. The linking group may also be a carbonyl such as in cyclohexyl phenyl ketone.

The term "arylalkyl" is used herein to refer to a subset of "aryl" in which the aryl group is attached through an alkyl group as defined herein. Examples include, but are not limited to, benzyl, phenylethyl and phenylpropyl groups.

"Substituted arylalkyl" defines a subset of "arylalkyl" wherein the aryl moiety of the arylalkyl group is substituted as defined herein for aryl groups.

The term "halogen" is used herein to refer to fluorine, bromine, chlorine and iodine atoms.

The term "hydroxy" is used herein to refer to the group -OH.

The term "amino" is used herein to refer to the group-NRR', where R and R' may independently be hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl or acyl.

The term "alkoxy" is used herein to refer to the -OR group, where R is a lower alkyl or substituted lower alkyl, wherein the alkyl and substituted lower alkyl groups are as described herein. Suitable alkoxy radicals include, for example, methoxy, ethoxy, t-butoxy, *etc.*

The term "aryloxy" is used herein to refer to the -OR group, wherein R is an aryl, substituted aryl, arylalkyl or substituted arylalkyl as described above. Examples include phenoxy, benzyloxy, phenethyloxy and substituted derivatives thereof.

The term "alkylamino" denotes secondary and tertiary amines wherein the alkyl groups may be either the same or different and may consist of straight or branches, saturated or unsaturated hydrocarbons.

The term "heterocyclic" is used herein to describe a monovalent group having a single ring or multiple condensed rings from 1-12 carbon atoms and from 1-4 heteroatoms selected from nitrogen, sulfur or oxygen within the ring. Such heterocycles include, for example, tetrahydrofuran, morpholine, piperidine, pyrrolidine, thiophene, pyridine, isoxazole, phthalimide, pyrazole, indole, furan, benzo-fused analogs of these rings, etc.

The term "substituted heterocyclic" as used herein describes a subset of "heterocyclic" wherein the heterocycle nucleus is substituted with one or more functional groups such as lower alkyl, acyl, halogen, alkylhalos (*e.g.*, CF_3), hydroxy, amino, alkoxy, alkylmino, acylamino, acyloxy, mercapto, *etc*.

The term "heterocyclicalkyl" is used herein to refer to a subset of "heterocylic" in which the heterocylcic group is attached through an alkyl group as defined herein.

"Substituted heterocyclicalkyl" defines a subset of "heterocyclicalkyl" wherein the heterocyclic moiety of the heterocyclicalkyl group is substituted as defined herein for heterocyclic groups.

The term "pharmaceutically acceptable salt" refers to those salts of compounds which retain the biological effectiveness and properties of the free bases and which are obtained by reaction with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and organic acids such as, for example, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutically acceptable salts include, for example, alkali metal salts, such as sodium and potassium, alkaline earth salts and ammonium salts.

The term "contacting" is used herein interchangeably with the following: combined with, added to, mixed with, passed over, incubated with, flowed over, *etc*. Moreover, the thiazolidinone compounds of present invention can be "administered" to a subject by any conventional method such as, for example, parenteral, oral, topical and inhalation routes as described herein.

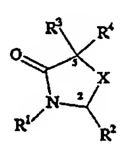
"An amount sufficient" or "an effective amount" is that amount of a given thiazolidinone analog which exhibits the binding/activity of interest or, which provides an improvement in gamete recruitment.

"EC_{50}" is the effective concentration, i.e., the concentration of a compound at which 50% of the maximal response of that obtained with FSH would be achieved.

"Non-competitive" refers to the nature of the agonist activity exhibited by the compounds of the invention, wherein the compounds act as agonists of and activate the FSH receptor without substantially reducing the magnitude of binding of FSH to the receptor. "Magnitude of binding" refers to the amount of FSH bound by a receptor population and/or the strength of the binding interaction between FSH and the FSH receptor.

The present invention is directed to novel thiazolidinone compounds which exhibit a range of pharmaceutical activities. In a presently preferred embodiment, the novel compounds are small molecule FSH receptor agonists. These compounds offer numerous advantages over the current state of the art (*i.e.*, gonadotrophins of urinary origin and recombinant FSH). For example, the compounds of the instant invention are inexpensive and both easily prepared and purified. Further, the compounds exhibit a range of activity regarding the FSH receptor. Such a manifold of compounds of differing activity provides an opportunity to the clinician to modulate the desired level of fertility induction by judicious choice of the fertility-inducing agent. In addition, the novel thiazolidinones, as small molecules, exhibit a pharmacokinetic profile which is distinct from that of conventional peptidic hormone preparations. The pharmacokinetic profile can be further modified by judicious choice of the route of administration and manipulating the nature of the substituents on the thiazolidinone nucleus.

In a first aspect, the present invention provides a compound having a formula:



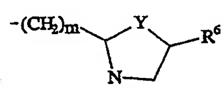
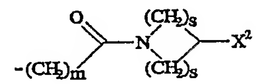
(I)

wherein,

R^1 is a member selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocyclic and substituted heterocylic groups;

R^2 is a member selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocylic groups;

R^3 and R^4 are independently members selected from the group including hydrogen, alkyl, $-(CH_2)_mCONR^5R^6$, $-(CH_2)_mOCONR^5R^6$,$-(CH_2)_mCH_2Y^2R^6$, $-(CH_2)_mCH{=}CHR^6$,

 , 

and $-(CH_2)_mCH_2NR^5CO(Y^3)_nR^6$;

R^5 and R^6 are independently members selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, arylalkyl, substituted arylalkyl, heterocyclicalkyl and substituted heterocyclicalkyl groups;

X is a member selected from the group consisting of S, S=O, and O=S=O;

Y is a member selected from the group consisting of O, S, and NH;

Y^2 is a member selected from the group consisting of CH_2, O, S, and NR^5;

Y^3 is a member selected from the group consisting of O and NR^6R^7;

R^7 is a member selected from the group consisting of hydrogen and lower alkyl;

X^2 is a member selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, phenyl, substituted phenyl, heterocyclic, substituted heterocyclic, arylalkyl, substituted arylalkyl, heterocyclicalkyl and substituted heterocyclicalkyl groups;

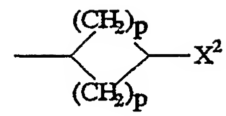
m is an integer from 0 to 3;

n is 0 or 1; and

s is 1 or 2.

In a presently preferred embodiment, the present invention provides a compound wherein,

R^5 and R^6 are independently members selected from the group consisting of hydrogen, $-(CH_2)_qX^2$, and



wherein

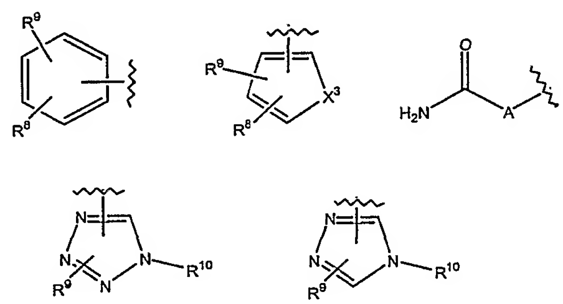
p is an integer from 1 to 2;

q is an integer from 0 to 5;

X^2 is a member selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, phenyl, substituted phenyl, heterocyclic, substituted heterocyclic, arylalkyl, substituted arylalkyl, heterocyclicalkyl and substituted heterocyclicalkyl groups; and

X is a member selected from the group consisting of S, S=O, and O=S=O.

More preferably, R^1 is a member selected from the group consisting of



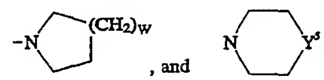
R^8 and R^9 are independently members selected form the group consisting of H, halogen, ketone, alkyl, substituted alkyl, phenyl, substituted phenyl, lower alkoxy, aryloxy, substituted aryloxy, carboxylic acid, carboxylic acid amide, sulfonic acid, sulfonic acid amide, alkynyl, substituted alkynyl and $-CONR^1(CH_2)_tZ$ wherein t is an integer from one to four;

R^{10} is a member selected from the group consisting of H and lower alkyl;

A is a member selected from the group consisting of C_1-C_4 alkyl and substituted C_1-C_4 alkyl, wherein each carbon atom is independently substituted with members selected from the group consisting of H, amino, alkyl, substituted alkyl, spirocyclic alkyl, substituted spirocyclic alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocyclic, and substituted heterocyclic groups;

X^3 is a member selected from the group consisting of O, S, SO, SO_2 and NR^{10};

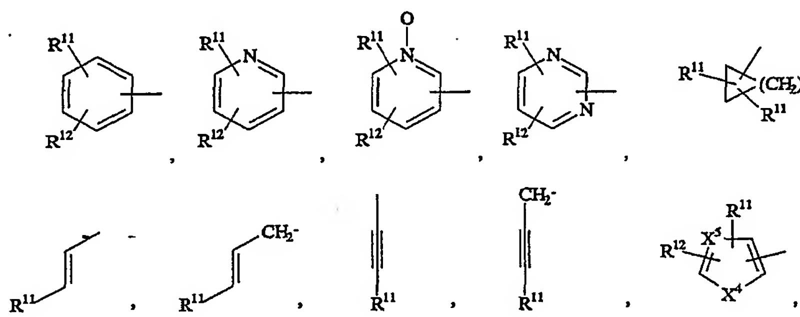
Z is a member selected from the group consisting of alkylamino, dialkylamino,



w is an integer from 1 to 3;

Y^5 is a member selected from the group consisting of O, S and NR^{10};

R^2 is a member selected from the group consisting of



wherein,

R^{11} and R^{12} are independently members selected from the group consisting of H, halogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, phenyl, substituted phenyl, aryloxy, substituted aryloxy, alkynyl, substituted alkynyl, nitro, cyano, aminoarylalkyl and substituted aminoarylalkyl;

u is an integer from 1 and 4;

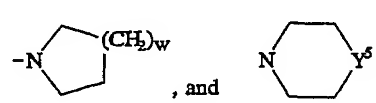
X^4 is a member selected from the group consisting of O, S, NR^{13}, and CR^{13};

X^5 is a member selected from the group consisting of O, S, NH, and CH;

R^{13} is a member selected from the group consisting of H, and lower alkyl.

More preferably, R^8 and R^9 are independently members selected form the group consisting of H, halogen, ketone, alkyl, substituted alkyl, carboxylic acid amide, sulfonic acid amide and alkynyl and $-CONR^1(CH_2)_tZ$ wherein t is an integer from one and four; wherein

Z is a member selected from the group consisting of alkylamino, dialkylamino,



w is an integer from 1 to 5;

Y^5 is a member selected from the group consisting of O, S, and NR^{10};

R^{10} is a member selected from the group consisting of H, and lower alkyl.

In another preferred embodiment, the present invention provides a compound wherein,

R^{11} and R^{12} are independently members selected from the group consisting of hydrogen, halogen, alkoxy, substituted alkoxy, aryloxy, $-\equiv-R^{14}$, and $-X^6-(CH_2)_v R^{14}$ wherein

R^{14} is a member selected from the group consisting of phenyl, substituted phenyl, alkyl, alkenyl, cyloalkyl, cycloalkenyl, $CH_2(X^7)_zR^{15}$, $CONHR^{15}$, COR^{15}, pyridine, thiophene, furan, pyrrole and phenylsulfonyl;

X^6 is a member selected from the group consisting of O, S, NH, and CH_2O;

X^7 is a member selected from the group consisting of O, S, and NR^{14};

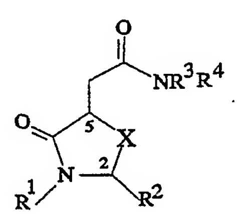
R^{15} is a member selected from the group consisting of H, alkyl and phenyl;

v is an integer from 0 to 3; and

z is 0 or 1.

In yet a further preferred embodiment, the present invention provides a compound wherein, when substituent R^4, on C-5, is H, and a second substituent at C-5 (R^3) is not H, said substituent R^3 on C-5 and substituent R^2 on C-2 are oriented in a *cis* manner.

In a second aspect, the present invention provides novel thiazolidinones having the formula:



(III)

wherein,

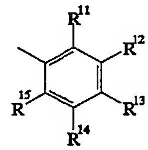
R^1 is a member selected from the group consisting of aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocyclic and substituted heterocyclic groups;

R^2 is a member selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic groups;

R^3 and R^4 are independently members selected from the group consisting of hydrogen, alkyl, substituted alkyl, arylalkyl, substituted arylalkyl, heterocyclic and substituted heterocyclic groups; and

X is a member selected from the group consisting of S, S=O and O=S=O.

In a presently preferred embodiment of this aspect of the invention, R^1 is aryl or substituted aryl. In another preferred embodiment, R^1 is phenyl or substituted phenyl. In a further preferred embodiment, R^1 is substituted phenyl as in Formula (IV)



(IV)

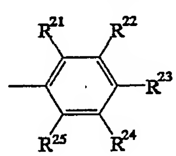
wherein R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are independently members selected from the group consisting of H, halogen, lower alkyl, substituted lower alkyl, phenyl, lower alkoxy, aryloxy, substituted aryloxy, carboxyl, ester and amide groups.

In other preferred embodiments, R^1 is a substituted phenyl according to Formula (IV) and R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are independently members selected from the group consisting of H, halogen, substituted alkyl, ketone, ester, amide and nitro groups.

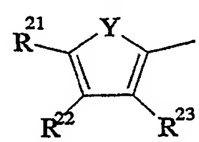
In still further preferred embodiments, R^1 is substituted phenyl according to Formula (IV) and R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are independently members selected from the group consisting of H, halogen and amide groups.

In another presently preferred embodiment, R^2 is a member selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic groups. In another preferred embodiment, R^2 is an aryl group. A preferred aryl group is the phenyl group and a preferred substituted aryl group is a substituted phenyl group.

In a further preferred embodiment, R^2 is a substituted phenyl according to Formula (V) or a five-membered ring according to Formula (VI)



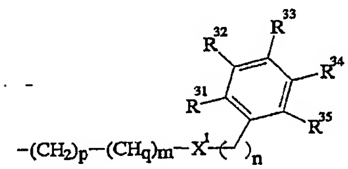
(V)



(VI)

wherein R^{21}, R^{22}, R^{23}, R^{24}, R^{25} are members independently selected from the group consisting of H, halogen, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, phenyl, substituted phenyl, aryloxy, substituted aryloxy, alkynyl, substituted alkynyl and nitro groups. Preferred aryloxy groups are phenoxy and benzyloxy and preferred substituted aryloxy groups are substituted phenoxy and substituted benzyloxy. Y is a member selected from the group consisting of $-CH_2-$, $-O-$, $-S-$ and NR^{26} wherein R^{26} is H or lower alkyl.

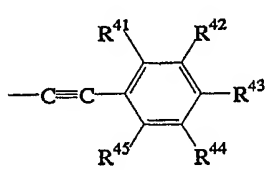
In a further preferred embodiment, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} are independently members selected from the group consisting of H, halogen, lower alkoxy and substituted aryl groups according to Formula (VII)



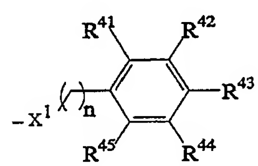
(VII)

wherein R^{31}, R^{32}, R^{33}, R^{34} and R^{35} are members independently selected from the group consisting of hydrogen, halogen, nitro and trifluoromethyl, alkyl, substituted alkyl, alkoxy and hydroxy. X^1 is a member selected from the group consisting of O, NR^{36}, S, C, CH and CH_2; R^{26} is H or lower alkyl; m is an integer from 0 to 5; n is an integer from 0 to 3, p is an integer from 0 to 3 and q is an integer from 0 to 2. When $q < 2$, a multiple bond exists between CH_q and X^1.

In certain presently preferred embodiments, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} are independently chosen from hydrogen and the groups according to Formulae (VIII) and (IX):



(VIII)



(IX)

wherein R^{41}, R^{42}, R^{43}, R^{44} and R^{45} are members independently selected from the group consisting of hydrogen, halogen, nitro and trifluoromethyl. In Formula (VIII), n is an integer from 0 to 3 and X^1 is O or NH.

In yet a further preferred embodiment, R^3 and R^4 are the same or different and are members independently selected from the group consisting of H and structures according to Formula (X):

$$-(CH_2)_s-X^2$$

(X) .

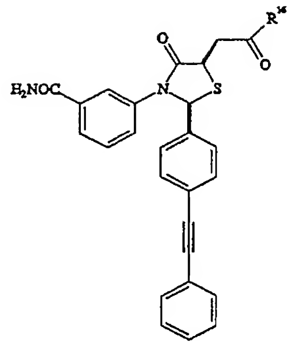
wherein s is an integer from 0 to 5, preferably from 1 to 5. X^2 is a member selected from the group consisting of aryl, substituted aryl, heterocyclic and substituted heterocyclic. In a further preferred embodiment, X^2 is heterocyclic or substituted aryl. In still further preferred embodiments, X^2 is phenyl, substituted phenyl, indole or substituted indole.

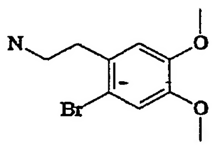
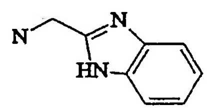
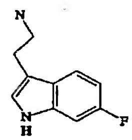
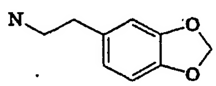
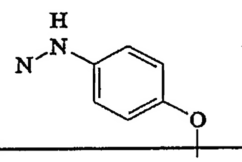
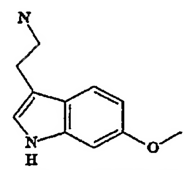
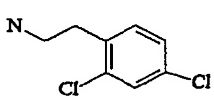
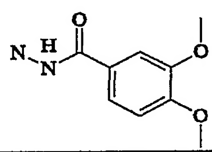
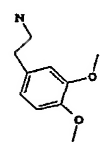
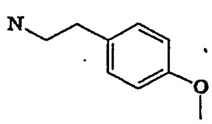
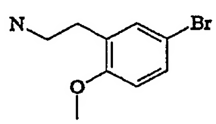
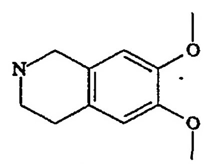
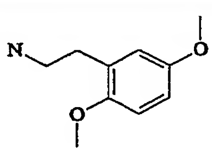
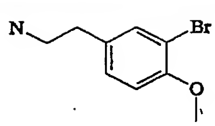
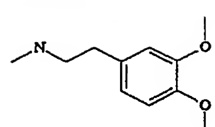
Due to the chiral carbons at positions 2 and 5 (*i.e.*, C-2 and C-5) of the thiazolidinone ring structure (*see*, for example, Formula III), the compounds of the invention can exist in a number of different isomeric and stereoisomeric forms. The configuration of C-2 and C-5 can be such that their substituents are in either a *cis* or *trans* configuration. In preferred embodiments, the compounds exist in the *cis* configuration. Additionally, the combination of absolute configurations available to C-2 and C-5 can take any one of four permutations. Thus, the thiazolidinone nucleus can be 2S, 5S; 2R, 5R; 2S, 5R; or 2R, 5S. Presently preferred embodiments are those in which the configuration at C-2 and C-5 are 2S, 5R.

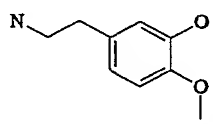
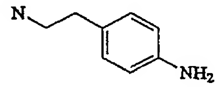
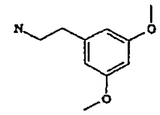
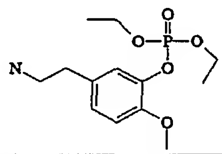
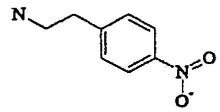
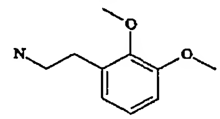
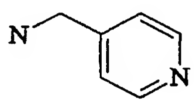
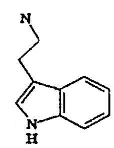
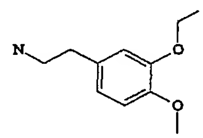
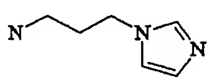
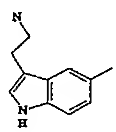
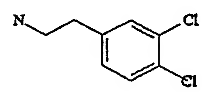
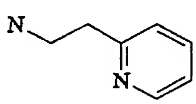
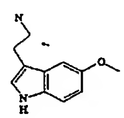
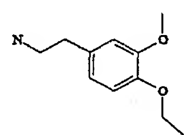
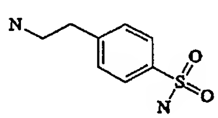
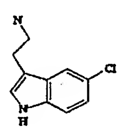
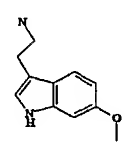
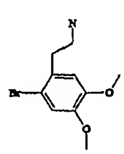
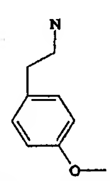
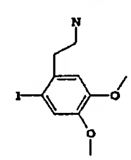
The compounds of the present invention can be used for diverse pharmaceutical applications including, for example, CNS antiischemic agents, agents with antipsychotic or other psychoactive properties, antimicrobial agents and mammalian fertility regulating agents. When used as mammalian fertility regulating agents, the thiazolidinones are preferably agonists of the FSH receptor.

Examples of presently preferred thiazolidinones having FSH agonist activity are displayed in Tables I-VI. The EC_{50} values of the compounds displayed in Tables I-VI are less than about 500 nM.

Table I.



R^{16}	R^{16}	R^{16}
		
		
		
		
		

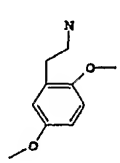
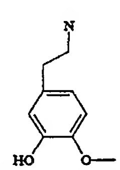
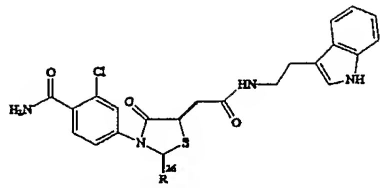
		

Table II.



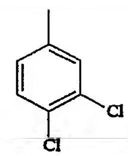
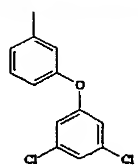
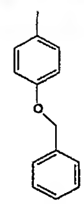
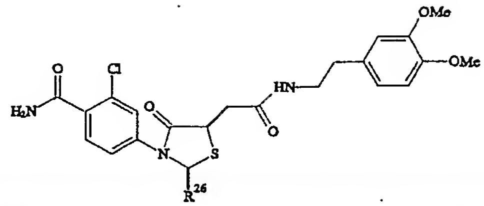
R^{26}	R^{26}
	
	

Table III.



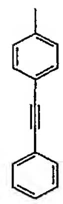
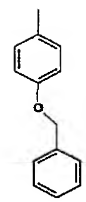
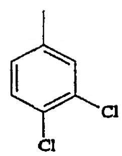
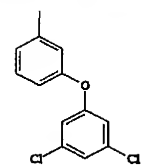
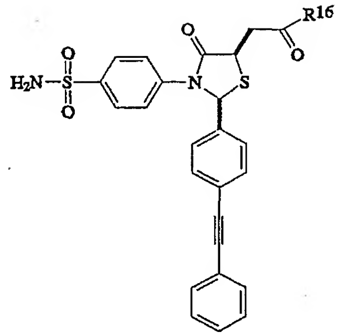
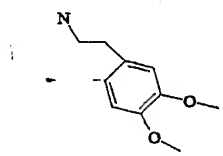
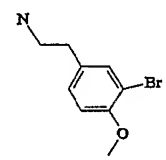
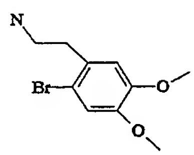
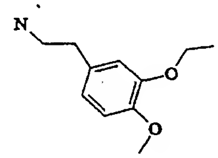
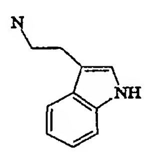
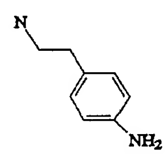
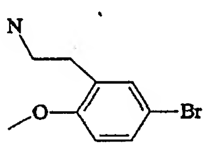
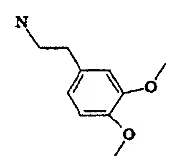
R^{26}	R^{26}
	
	

Table IV.



R^{16}	R^{16}
	
	
	
	

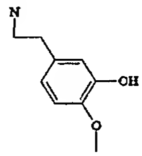
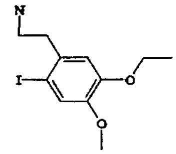
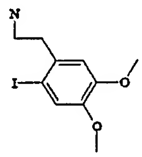
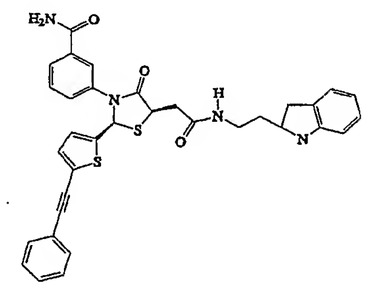
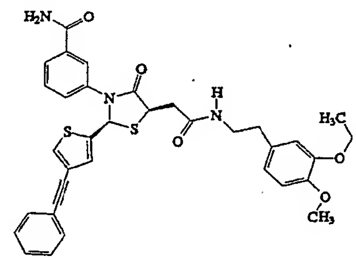
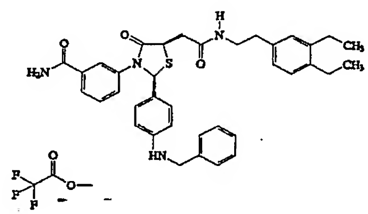
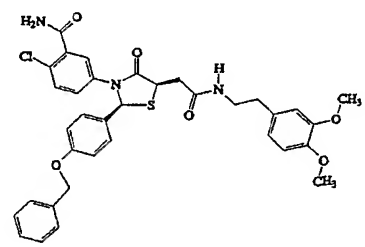
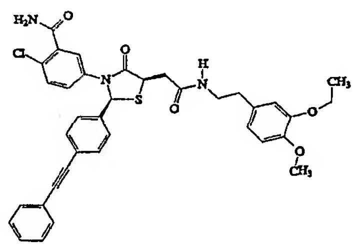
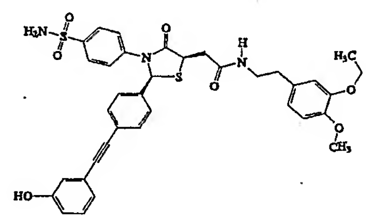
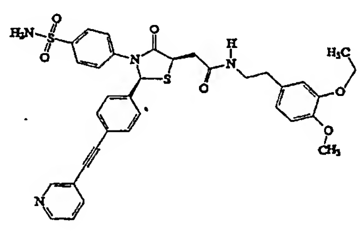
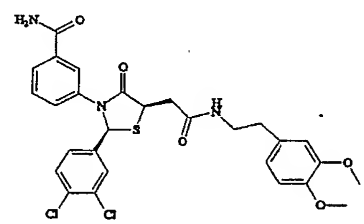
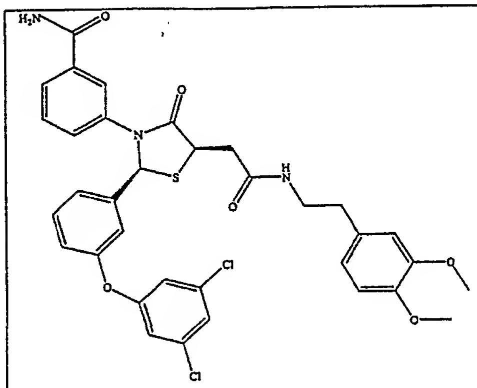
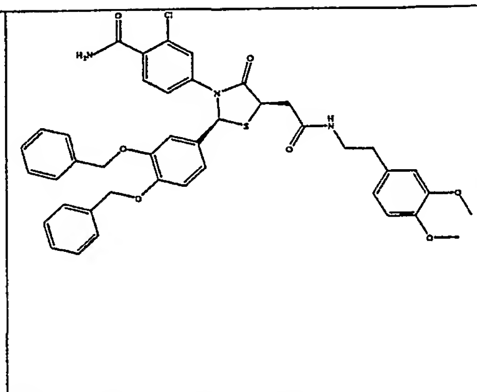
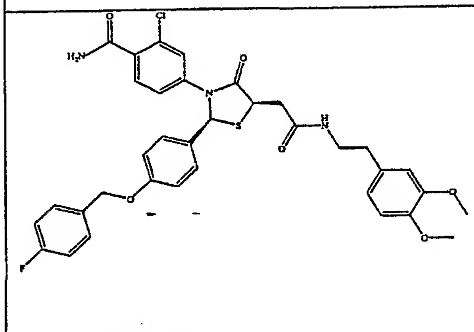
	
	

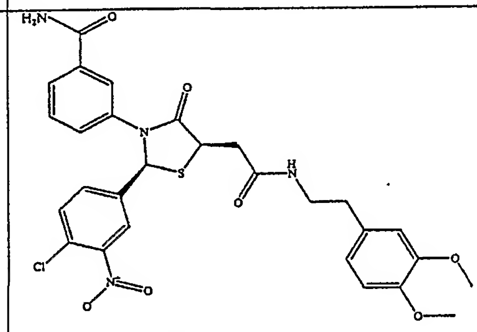
Table V.

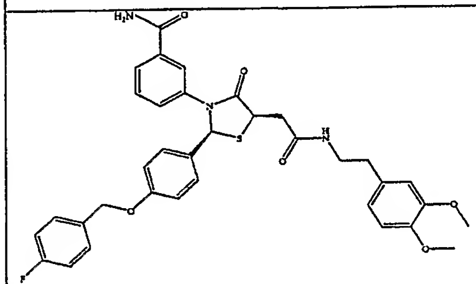
	
	
	
	

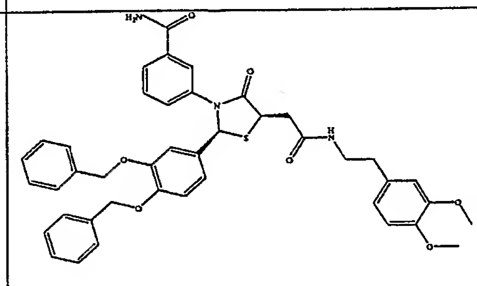


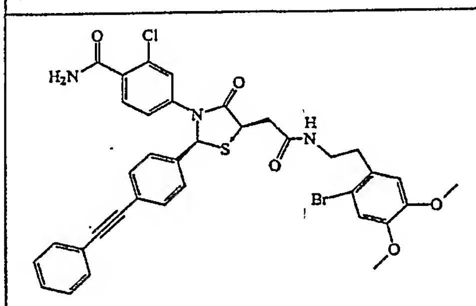


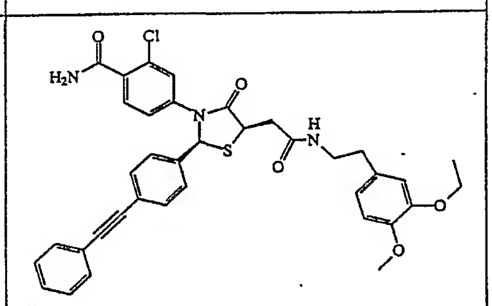


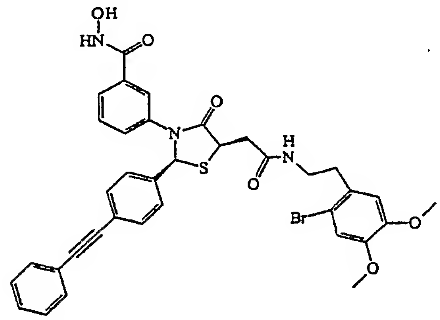
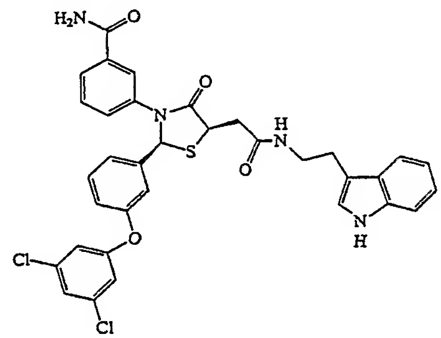
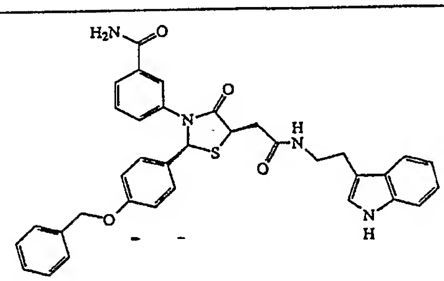
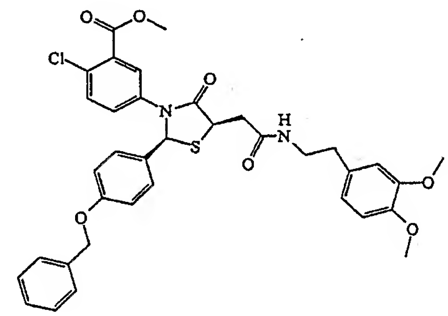
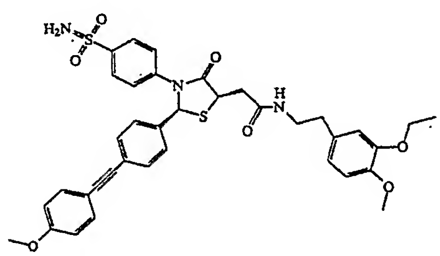
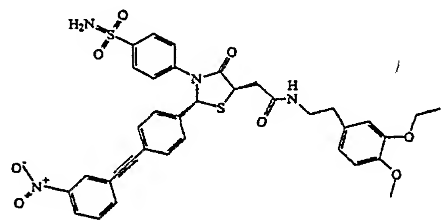
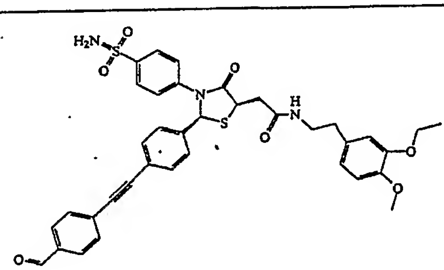
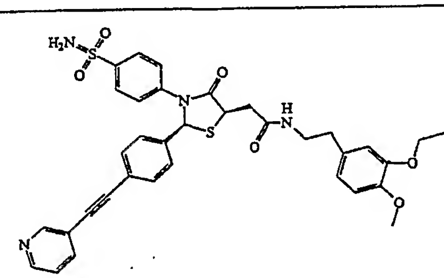


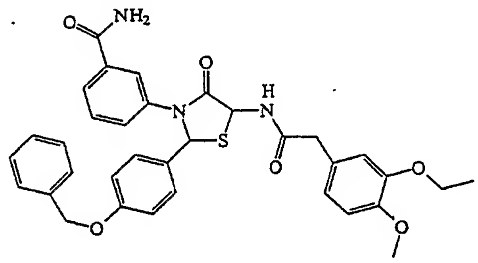
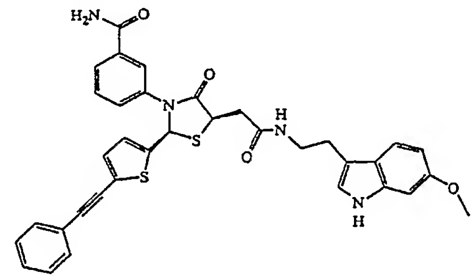
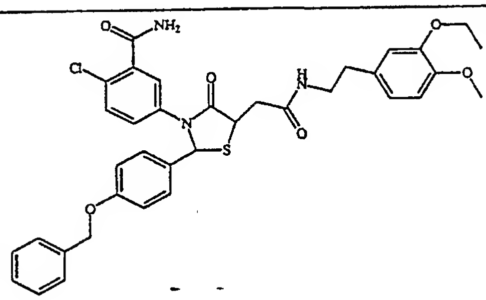
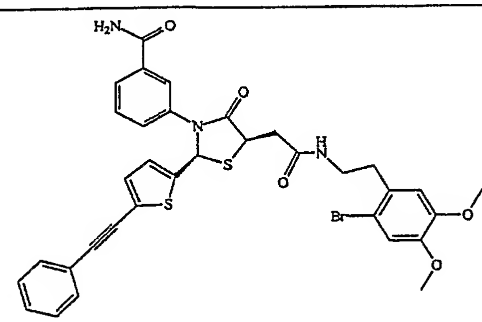
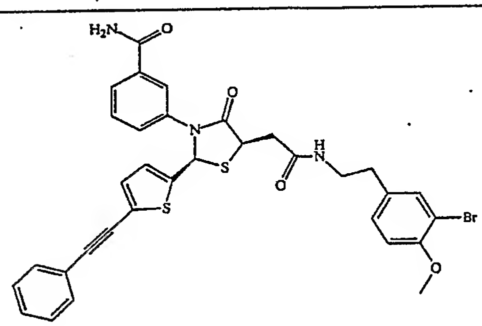
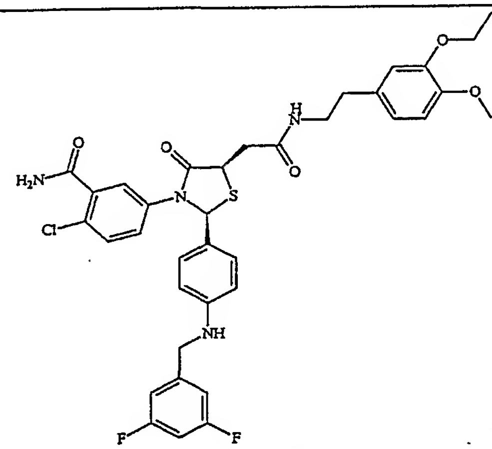








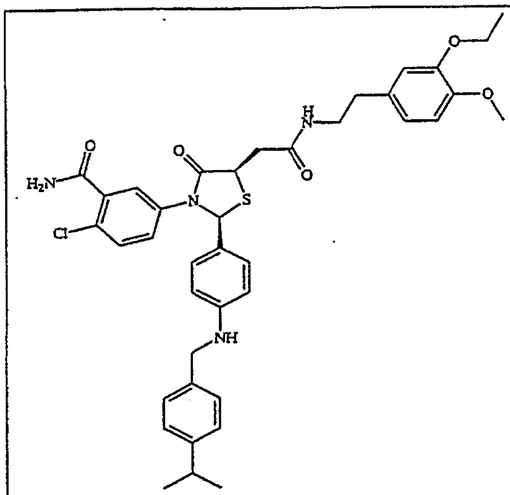
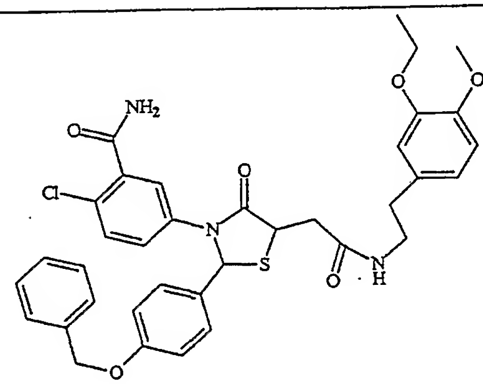
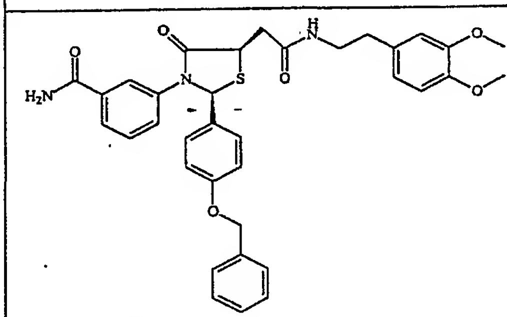
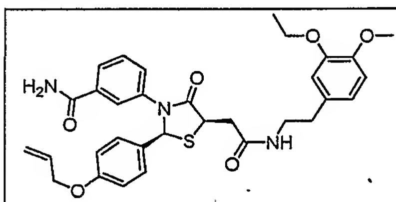
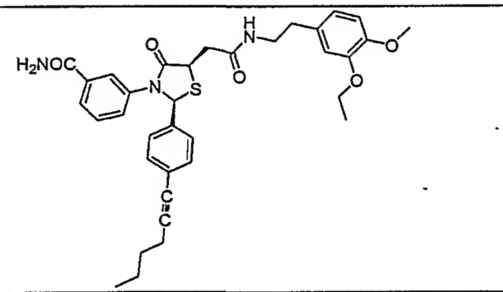
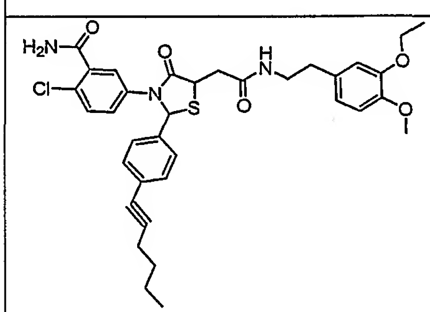
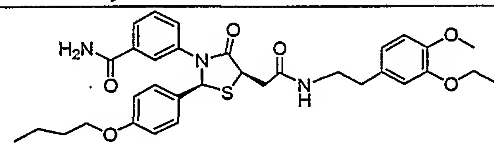
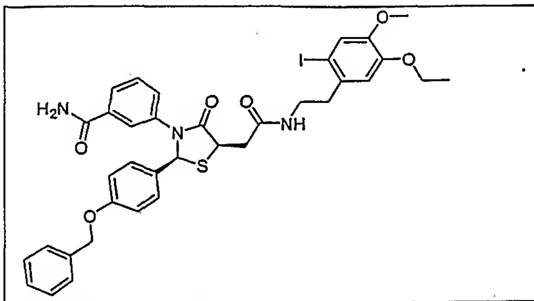
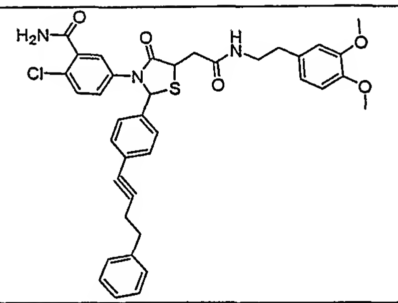
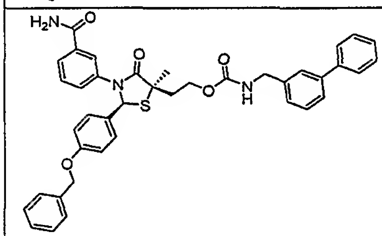
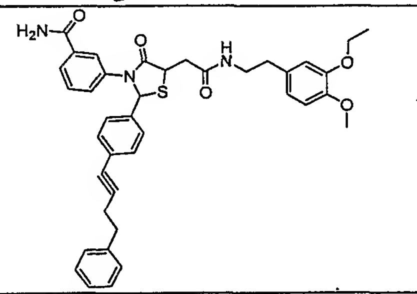
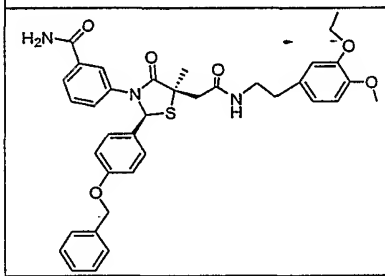
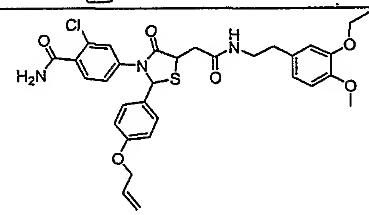
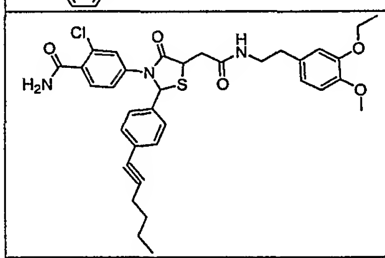
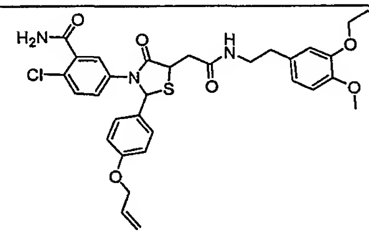
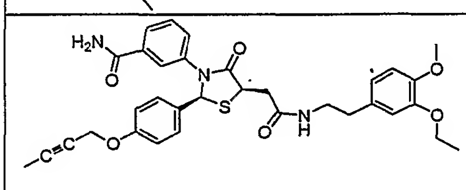
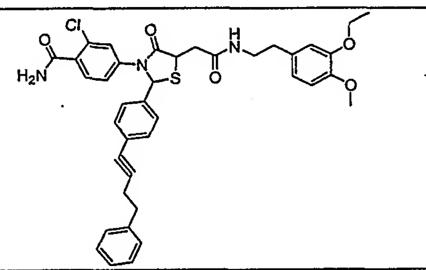
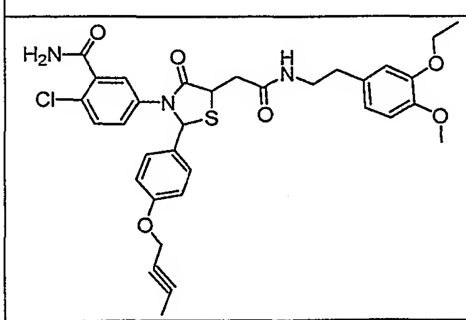
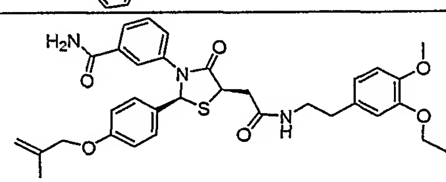
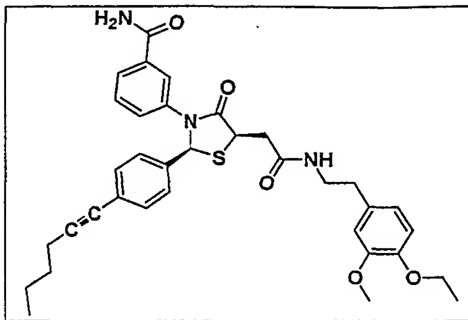
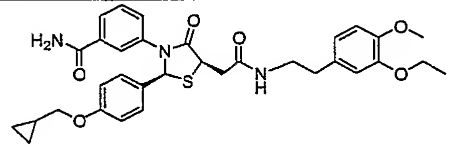
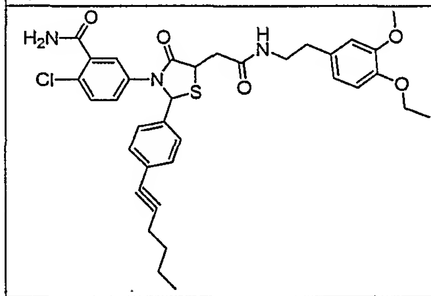
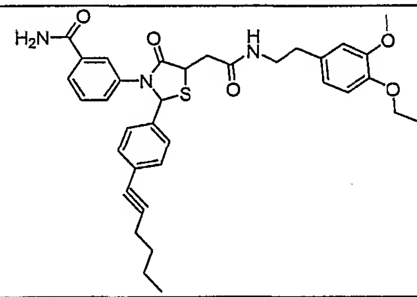
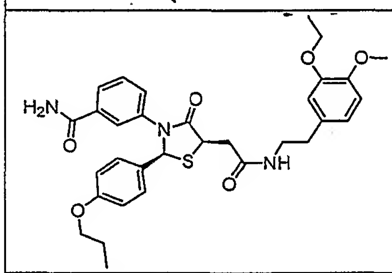
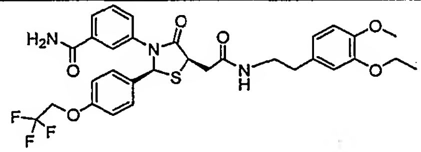
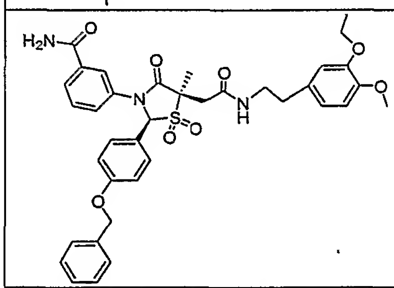
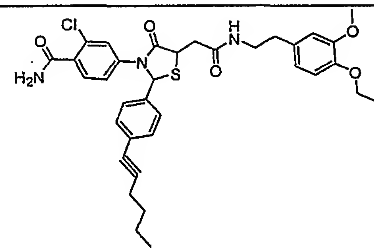
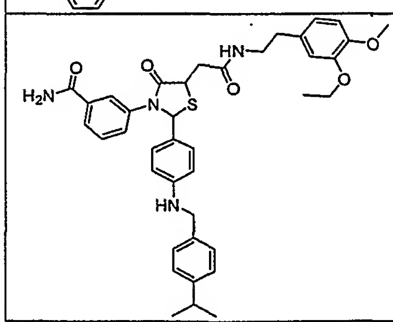
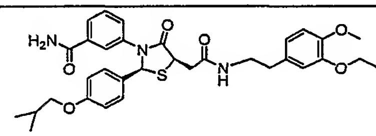
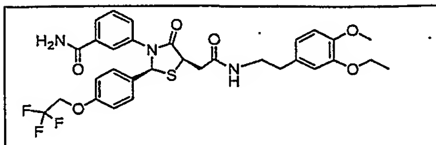
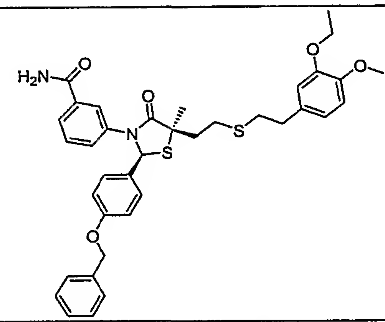
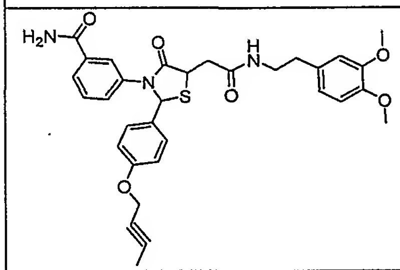
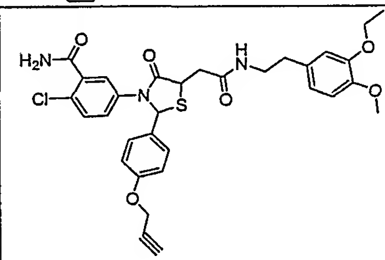
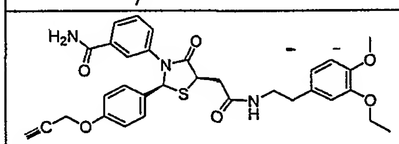
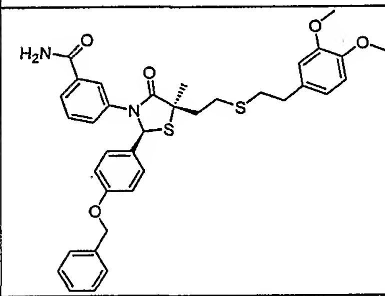
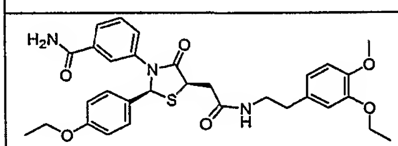
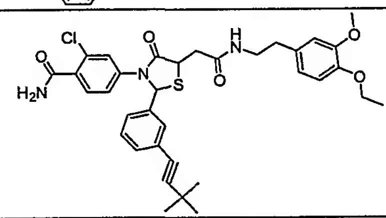
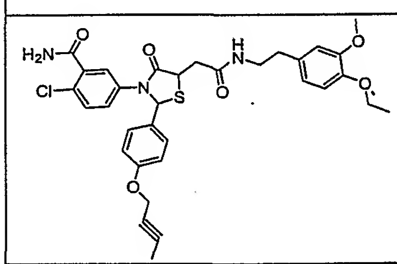
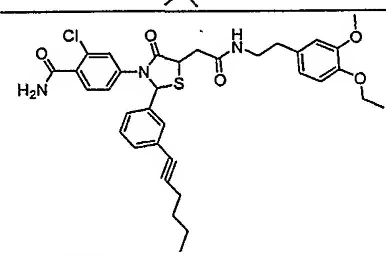
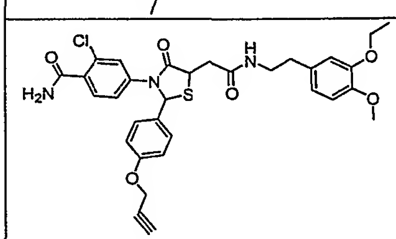
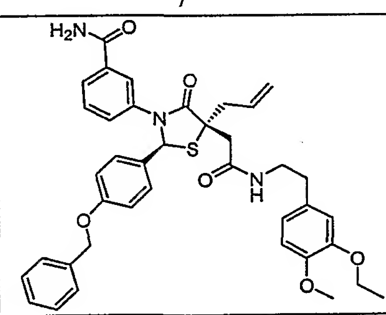
	
	

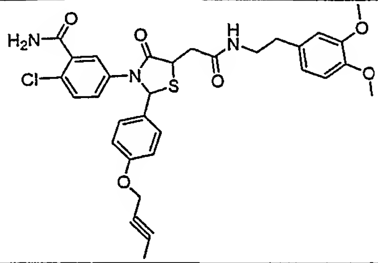
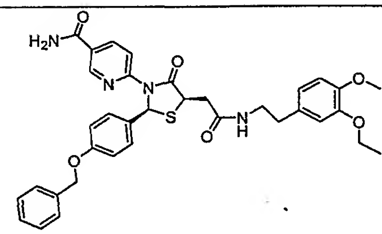
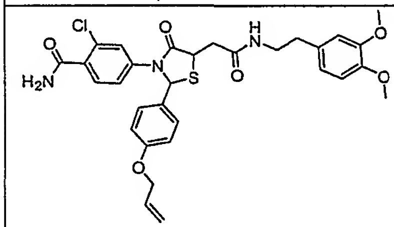
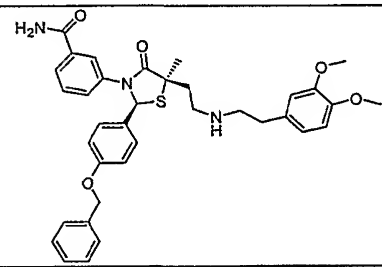
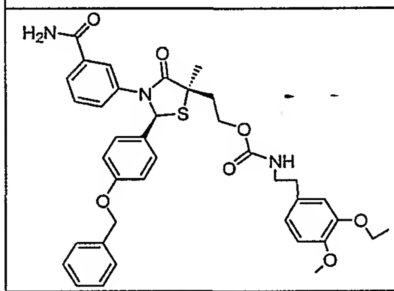
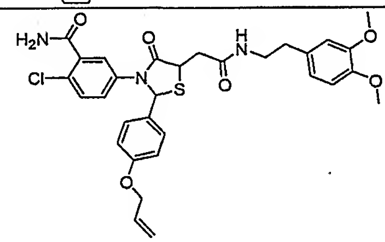
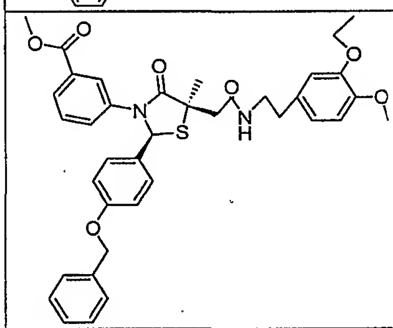
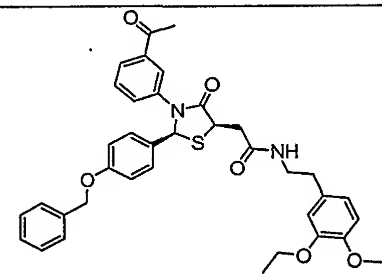
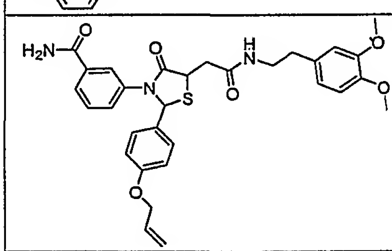
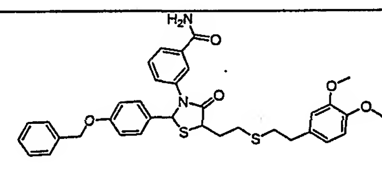
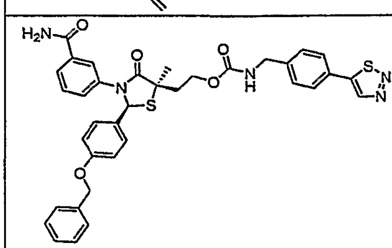
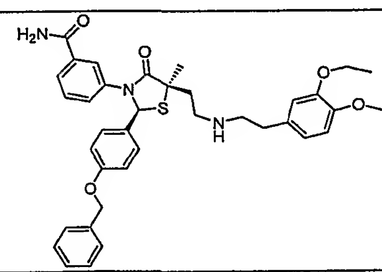
Table VI.

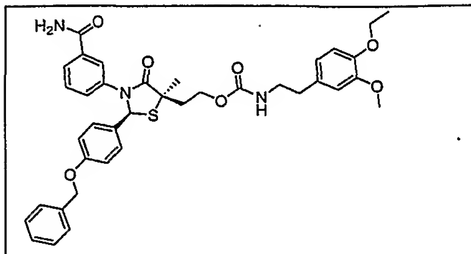
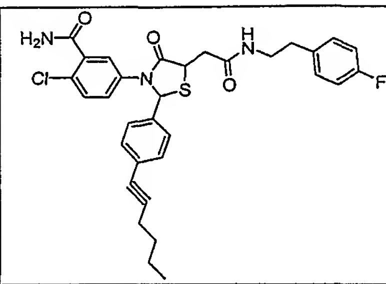
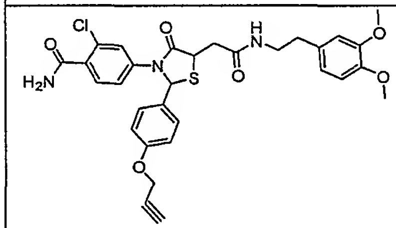
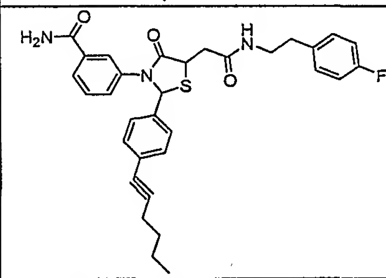
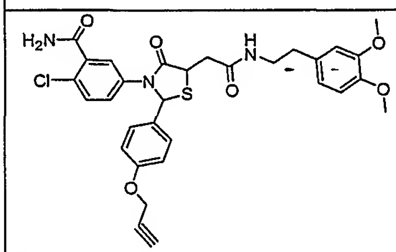
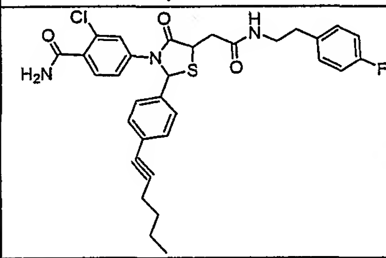
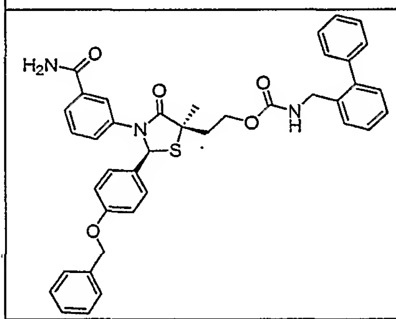
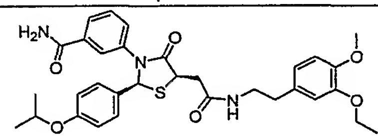
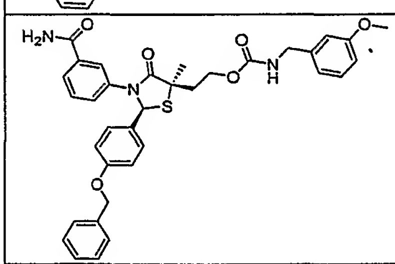
	
	

In another aspect, the invention provides a class of FSH receptor agonists, wherein the receptor agonist activity is noncompetitve with FSH. In a preferred embodiment, the non-competitive FSH agonists are organic molecules with a molecular weight of from about 50 daltons to about 1000 daltons, more preferably from about 200 daltons to about 1000 daltons. In another preferred embodiment, the invention provides

for pharmaceutical formulations containing a FSH receptor agonist which is non-competitive with FSH. In this aspect, the invention provides regulators of mammalian fertility which are useful in the diverse applications described herein for the thiazolidinones of the invention.

B. Pharmaceutical Compositions and Uses

In another embodiment, the present invention provides pharmaceutical compositions which contain one or more of the compounds of the invention in conjunction with pharmaceutically acceptable excipients, carriers, diluents, *etc.* The pharmaceutical compositions can also contain other agents which are themselves pharmacologically active and which serve to enhance, supplement, decrease or otherwise regulate the pharmacological effect of the pharmaceutical compositions.

The compounds, *i.e.,* thiazolidinones, of the present invention can be administered to a mammal, *e.g.*, a human patient, alone, in the form of a pharmaceutically acceptable salt, or in the form of a pharmaceutical composition where the compound is mixed with suitable carriers or excipient(s) in a therapeutically effective amount. Further, the compounds and compositions of the invention can be administered to induce greater fertility in the patient or they can be administered to stimulate the production of ova which will be removed, fertilized *in vitro* and implanted in the patient or a surrogate. There are a number of art accepted techniques and technologies for accomplishing both of these goals. *See*, for example, Jennings, *et al.*, "*in vitro* fertilization: A review of drug therapy and clinical management." *Drugs* **52**:313-343 (1996), the disclosure of which is incorporated herein by reference.

By analogy to the demonstrated efficacy of gonadotrophins on the Sertoli cell, that is, the male equivalent of the ovarian granulosa cells, the compounds and compositions of the present invention can be used for the treatment of male, as well as female, infertility. *See*, for example, Reichert, *et al.*, "The follicle stimulating hormone (FSH) receptor in testis: interaction with FSH, mechanism of signal transduction, and properties of the purified receptor," *Biol. Reprod.* **40**:13-26 (1989), the disclosure of which is incorporated herein by reference.

The compounds of this invention can be incorporated into a variety of formulations for therapeutic administration. More particularly, the compounds of the present invention can be formulated into pharmaceutical compositions by combination

with appropriate, pharmaceutically acceptable carriers or diluents, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, pills, powders, granules, dragees, gels, slurries, ointments, solutions, suppositories, injections, inhalants and aerosols. As such, administration of the compounds can be achieved in various ways, including oral, buccal, rectal, parenteral, intraperitoneal, intradermal, transdermal, intracheal, *etc.*, administration. Moreover, the compound can be administered in a local rather than systemic manner, for example, via injection of the compound directly into an ovary, often in a depot or sustained release formulation. In addition, the compounds can be administered in a targeted drug delivery system, for example, in a liposome coated with an organ surface receptor-specific antibody. Such liposomes will be targeted to and taken up selectively by the organ.

In pharmaceutical dosage forms, the compounds may be administered in the form of their pharmaceutically acceptable salts, or they may also be used alone or in appropriate association, as well as in combination with other pharmaceutically active compounds. In the interest of brevity, the discussion which follows is based on the use of the compounds of the invention as fertility-inducing agents. That pharmaceutical compositions containing the novel thiazolidinones are useful in other applications, and are not limited to use as fertility-inducing agents will be apparent to those of skill in the art. In these further applications, adjuncts which serve a purpose analogous to those discussed below (*i.e.*, enhance or supplement the thiazolidinone therapeutic activity) can be included within the formulation.

The thiazolidinone analogs of the present invention can be administered alone, in combination with each other, or they can be used in combination with other known compounds (*e.g.*, fertility-inducing agent, such as FSH, LH and hMG). Other agents which can be included in the pharmaceutical compositions include ovulation adjuncts such as, for example, cytokines (*e.g.*, IGF-1 and TGF-β) and narrow action oligopeptides (*e.g.*, activins, inhibins and follistatins). *See*, for example, Gast, "Evolution of clinical agents for ovulation induction." *Am. J. Obstet Gynecol.* **172**:753-59 (1995), Meldrum, "Ovarian stimulation for assisted reproduction," *Curr. Opin. Obstet. Gynecol.* **8**: 166-70 (1996), which are incorporated herein by reference. Other ovulation adjuncts are known to those of skill in the art and are useful with the compounds of the present invention.

A number of suitable formulations for use in the present invention are found in *Remington's Pharmaceutical Sciences* (Mack Publishing Company, Philadelphia, PA, 17th ed. (1985), which is incorporated herein by reference. Moreover, for a brief review of methods for drug delivery, *see*, Langer, *Science* **249**:1527-1533 (1990), which is incorporated herein by reference. The pharmaceutical compositions described herein can be manufactured in a manner that is known to those of skill in the art, *i.e.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. The following methods and excipients are merely exemplary and are in no way limiting.

For injection, the compounds can be formulated into preparations by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives. Preferably, the compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining with pharmaceutically acceptable carriers that are well known in the art. Such carriers enable the compounds to be formulated as tablets, pills, dragees, capsules, emulsions, lipophilic and hydrophilic suspensions, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing the compounds with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating

agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from propellant-free, dry-powder inhalers. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampules or in multidose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or

emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, carbowaxes, polyethylene glycols or other glycerides, all of which melt at body temperature, yet are solidified at room temperature.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various types of sustained-release materials have been established and are well known by

those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in a therapeutically effective amount. The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician. Determination of an effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

For any compound used in the method of the invention, a therapeutically effective dose can be estimated initially from cell culture assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the EC_{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Initial dosages can also be estimated from *in vitro* or *in vivo* data.

Initial dosages can also be formulated by comparing the effectiveness of the compounds described herein in cell culture assays with the effectiveness of known drugs. For instance, when used as fertility agents, initial dosages can be formulated by comparing the effectiveness of the compounds described herein in cell culture assays with the effectiveness of known fertility agents such as hMG or FSH. In this method, an initial dosage can be obtained by multiplying the ratio of effective concentrations obtained in cell culture assay for the compound of the present invention and a known fertility drug by the effective dosage of the known fertility drug. For example, if a compound of the present invention is twice as effective in cell culture assay as hMG (*i.e.*, the EC_{50} of that compound is equal to one-half the EC_{50} of hMG in the same assay), an initial effective dosage of the compound of the present invention would be one-half the known dosage for hMG. Using these initial guidelines one having ordinary skill in the art could determine an effective dosage in humans or other mammals.

Moreover, toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, by determining the LD_{50} (the dose required to cause death in 50% of the subjects tested) and the ED_{50} (the dose that produces a defined effect in 50% of the subjects tested). The dose ratio between toxic and therapeutic effect is the therapeutic index and can be expressed as the ratio between LD_{50} and ED_{50}. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a dosage range that is appropriate for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. *See,* for example, Fingl, *et al.*, In: *The Pharmacological Basis of Therapeutics*, Ch. 1, p. 1 (1975).

Dosage amount and interval may be adjusted individually to provide plasma levels of the active compound which are sufficient to maintain therapeutic effect. Usual patient dosages for oral administration range from about 50-2000 mg/kg/day, commonly from about 100-1000 mg/kg/day, preferably from about 150-700 mg/kg/day and most preferably from about 250-500 mg/kg/day. Preferably, therapeutically effective serum levels will be achieved by administering multiple doses each day. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration. One having skill in the art will be able to optimize therapeutically effective local dosages without undue experimentation.

When used as fertility-inducing agents in the female, the compositions of the invention can be evaluated for their effectiveness by any of a number of art accepted parameters including number of follicles, number of oocytes, number of transferrable embryos, number of pregnancies, the total dose administered and the treatment length. Similarly accepted criteria are available for evaluating the safety of a fertility-inducing agent including incidence of ovarian hyperstimulation and incidence of multiple gestation. When used to enhance fertility in the male, effectiveness can be adduced by increased sperm count, sperm motility and the like. Additional criteria and methods for assessing

the efficacy of a thiazolidinone-containing pharmaceutical composition, when used as a fertility-inducing agent or for another purpose, will be apparent to those of skill in the art.

The thiazolidinones can be incorporated into the pharmaceutical formulation as mixtures of diastereomers, mixtures of enantiomers or as stereochemically distinct compounds. The origin of the isomerism is the chirality of the carbons at positions 2 and 5 of the thiazolidinone ring structure (Formula I). For example in one preferred embodiment, the thiazolidinone component of the pharmaceutical composition is a mixture of *cis* and *trans* isomers. In another preferred embodiment, the mixture of *cis* and *trans* isomers is enriched in the *cis* isomer relative to the *trans* isomer. In a further preferred embodiment, the thiazolidinone is present as the substantially pure *cis* isomer.

The stereochemistry of the carbon atoms at positions 2 and 5 of the ring is yet another feature of the thiazolidinone constituent which can be varied. In a preferred embodiment, the thiazolidinone constituent is a mixture of the 2S, 5R and 5S, 2R isomers. In a more preferred embodiment, the thiazolidinone constituent is enriched in the 2S, 5R isomer. In still further preferred embodiments, the thiazolidinone constituent is substantially pure 2S, 5R.

In addition to the foregoing, the compounds of the invention are useful *in vitro* as unique tools for understanding the biological role of FSH, including the evaluation of the many factors thought to influence, and be influenced by, the production of FSH and the interaction of FSH with the FSH-R (*e.g.*, the mechanism of FSH signal transduction/receptor activation). The present compounds are also useful in the development of other compounds that interact with the FSH-R, because the present compounds provide important structure-activity relationship (SAR) information that facilitate that development.

Compounds of the present invention that bind to the FSH receptor can be used as reagents for detecting FSH receptors on living cells, fixed cells, in biological fluids, in tissue homogenates, in purified, natural biological materials, *etc.* For example, by labelling such compounds, one can identify cells having FSH-R on their surfaces. In addition, based on their ability to bind the FSH receptor, compounds of the present invention can be used in *in situ* staining, FACS (fluorescence-activated cell sorting), western blotting, ELISA (enzyme-linked immunoadsorptive assay), *etc.* In addition, based on their ability to bind to the FSH receptor, compounds of the present invention can be

used in receptor purification, or in purifying cells expressing FSH receptors on the cell surface (or inside permeabilized cells).

The compounds of the invention can also be utilized as commercial research reagents for various medical research and diagnostic uses. Such uses can include but are not limited to: (1) use as a calibration standard for quantitating the activities of candidate FSH agonists in a variety of functional assays; (2) use as blocking reagents in random compound screening, *i.e.*, in looking for new families of FSH receptor ligands, the compounds can be used to block recovery of the presently claimed FSH compounds; (3) use in the co-crystallization with FSH receptor, *i.e.*, the compounds of the present invention will allow formation of crystals of the compound bound to the FSH receptor, enabling the determination of receptor/compound structure by x-ray crystallography; (4) other research and diagnostic applications wherein the FSH-receptor is preferably activated or such activation is conveniently calibrated against a known quantity of an FSH agonist, and the like; (5) use in assays as probes for determining the expression of FSH receptors on the surface of cells; and (6) developing assays for detecting compounds which bind to the same site as the FSH receptor binding ligands.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters which can be changed or modified to yield essentially the same results.

EXAMPLES

The following examples illustrate the preparation of three libraries of novel thiazolidinones. In brief, the thiazolidinones are constructed from three distinct components; an amino acid, an aldehyde and an amine. In each of the three libraries, the identity of one of these constituents is varied over the library. Example 1 details the assembly of a library in which the amino acid component is varied. In Example 2, the synthesis of a library in which the aldehyde component is varied is set forth. Example 3 illustrates a library, wherein the amine component is varied. Example 4 illustrates a scaled-up synthesis of one exemplary novel thiazolidinone. Example 5 sets forth the synthetic route to enantiomerically pure thiazolidinones from an enantiomerically pure mercaptosuccinic acid precursor. Example 6 details the synthesis of thiophene compounds

of the invention. Example 7 sets forth the synthesis of phenethylamine compounds of the invention. Example 8 details the synthesis of a benzyl ether derivative of the invention. Example 9 details the preparation of iodobenzyl derivatives of compounds of the invention. Example 10 illustrates the exchange of acetylene for iodine in the compound of Example 9. Example 11 illustrates the coupling of pyridine to the acetyline moiety of the compound of Example 10. Example 12 illustrates the derivatization of the carboxylic acid moiety of the compound of Example 11 with an amine. Example 13 illustrates the oxidation of the ring sulfur of a thiazolidinone compound of the invention. Example 14 details the experimental protocol for assaying the compounds of the invention for their ability to act as FSH antagonists. Example 15 illustrates an assay for determining whether the compounds of the invention compete with FSH for the FSH binding site.

Example 1

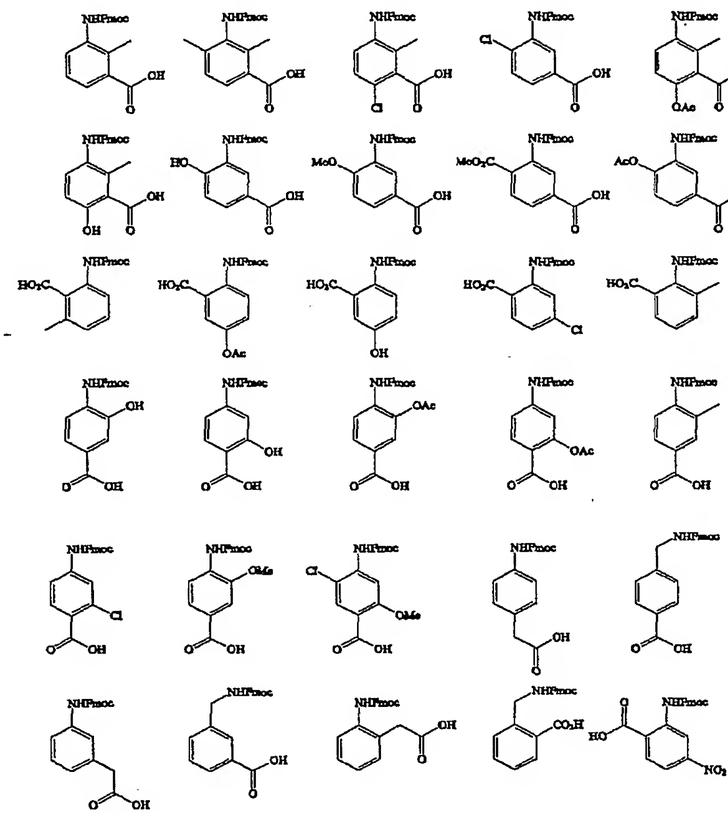
This example details the synthesis of a library of thiazolidinones in which the amino acid component is varied. To a 96 well parallel synthesis apparatus was added 50 mg of Argogel-Rink Amide-FMOC (0.33 mmol/g loading) to 30 of the wells. The resin was washed with dichloromethane (100 mL) and N,N-dimethylformamide (100 mL). The resin was then deprotected with 20% piperidine in N,N-dimethylformamide (1 mL) for 30 minutes. The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide. To each well was added 5 eq. of 30 different N-Fmoc protected amino acids (*see*, Table VI), 10 eq. of HATU, and 10 eq. of DIEA in DMP (1 mL) for 16 hours. The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide. The resin was then deprotected with 20% piperidine in N,N-dimethylformamide (1 mL) for 30 minutes. The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide.

The resin was then treated with 20 eq. of 4-(phenethynyl)benzaldehyde and 40 eq. of mercaptosuccinic acid in THF (1 mL) and heated at 60°C for 16 hours. The apparatus was cooled and washed with hot THF. The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide.

Each well was reacted with 20 eq. 3,4-dimethoxyphenethylamine (60 μL/well), 20 eq. DIEA (60 μL/well), and 20 eq. diethylcyanophosphate (60 μL/well) in DCM (1 mL) for 3 hours. The resin was washed exhaustively with THF, DMF, DCM, MeOH, DCM in sequence. The products were cleaved with 95% TFA/DCM for 1 hour,

drained and collected into a 96 well plate. The solvent was removed under reduced pressure on a speed vac overnight. Acetonitrile (1 mL/well) was added and removed by speed vac. Methanol (1 mL/well) was added and removed by Gene Vac. Submitted for biological assay at an estimated concentration of 8.25 μmol/well.

TABLE VI.



Example 2

This example illustrates the assembly of a library of the compounds of the novel thiazolidinones of the invention in which the structure of the aldehyde component is varied.

To a 250 mL peptide vessel was added 5.0 g of Argogel-Rink Amide--FMOC (0.33 mmol/g loading). The resin was washed with dichloromethane (100 mi) and N,N-dimethylformamide (100 mL). The resin was then deprotected with 20% piperidine in N,N-dimethylformamide (50 mL) for 30 minutes. The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide. 3-Aminobenzoic acid

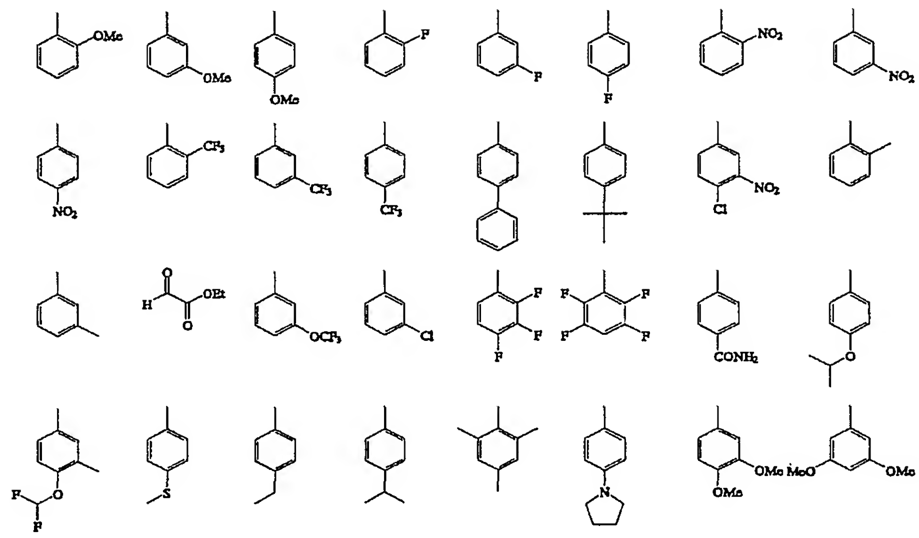
(N-Fmoc protected, 2,0 g, 5.6 mmol) was coupled to the resin with HATU (2.327 g, 6.1 mmol) and DIEA (1.07 mL, 6.1 mmol) in DMF (12 mL) for 16 hours. The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide. The resin was then deprotected with 20% piperidine in N,N-dimethylformamide (50 mL) for 30 minutes. The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide.

The resin was distributed into 96 wells on a parallel synthesis apparatus (~50 mg/well). To each well was added 20 eq. one of 96 different aldehydes (see below) and 40 eq mercaptosuccinic acid. THF (1 mL) was added to each well and heated at 70°C for 24 hours. The apparatus was cooled and each well was washed exhaustively with THF, DCM, DMF, DCM, MeOH, DCM, DMF in sequence.

Each well was reacted with 20 eq. 3,4-dimethoxyphenethylamine (60 μL/well), 20 eq. DIEA (60 μL/well), and 20 eq. diethylcyanophosphate (60 μL/well) in DCM (1 mL) for 3 hours. The resin was washed exhaustively with THF, DMF, DCM, MeOH, DCM in sequence. The products were cleaved with 95% TFA/DCM for 1 hour, drained and collected into a 96 well plate. The solvent was removed under reduced pressure on a speed vac overnight. Acetonitrile (1 mL/well) was added and removed by speed vac. Methanol (1 mL/well) was added and removed by Gene Vac. Submitted for biological assay at an estimated concentration of 8.25 μmol/well.

The manifold of structures which were derived from the various aldehyde constituents and the point at which these structures were attached to the thiazolidinone ring are displayed in Table VII.

TABLE VII.



Example 3

This example illustrates the assembly of a thiazolidinone library, wherein the amine component of the thiazolidinone is varied over the library.

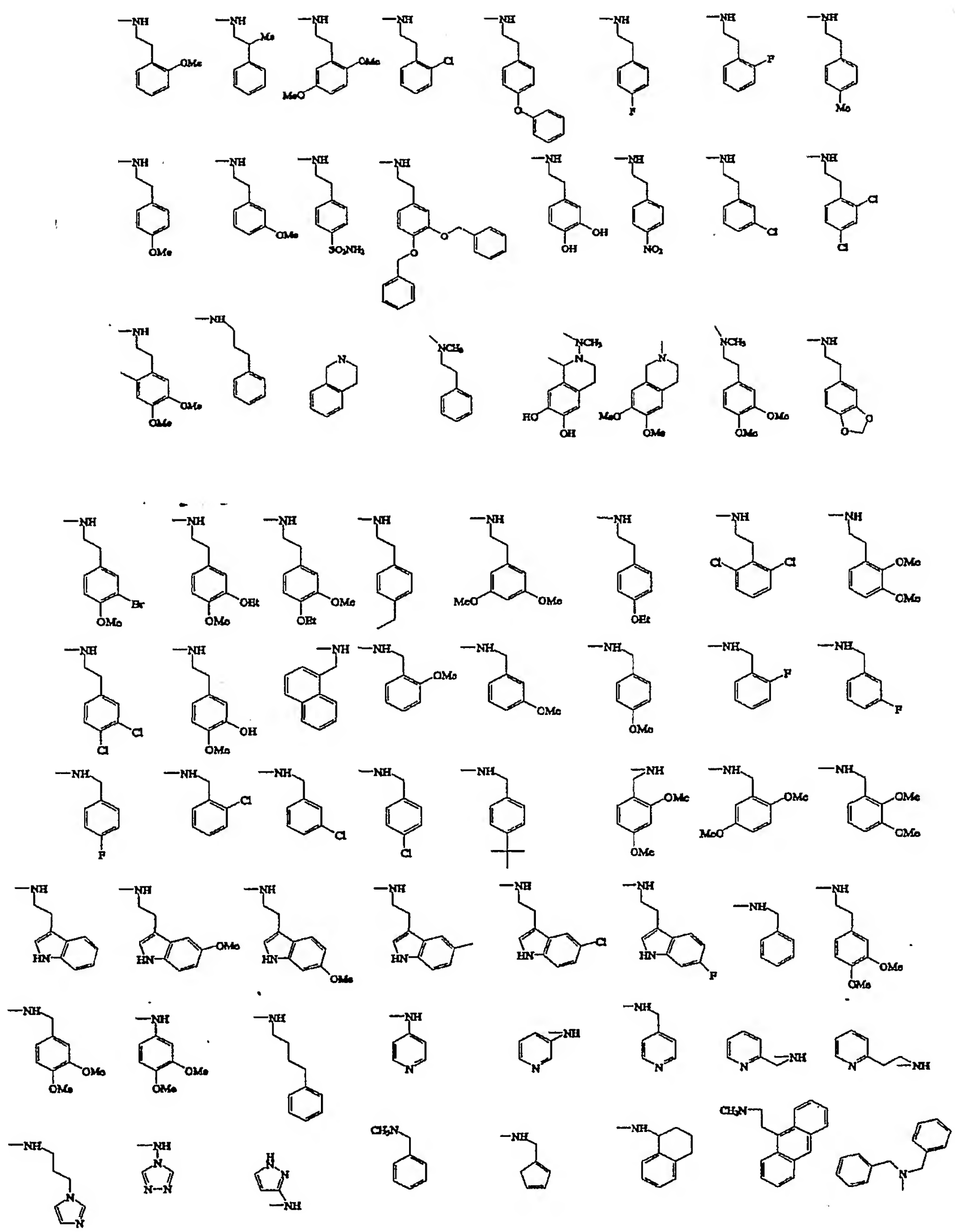
To a 250 mL peptide vessel was added 5.0 g of Argogel-Rink Amide-FMOC (0.33 mmol/g loading). The resin was washed with dichloromethane (100 mL) and N,N-dimethylformamide (100 mL). The resin was then deprotected with 20% piperidine in N,N-dimethylformamide (50 mL) for 30 minutes. The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide. 3-Aminobenzoic acid (N-Fmoc protected, 2.0 g, 5.6 mmol) was coupled to the resin with HATU (2.327 g, 6.1 mmol) and DMA (1.07 mL, 6.1 mmol) in DMP (12 mL) for 16 hours. The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide. The resin was then deprotected with 20 % piperidine in N,N-dimethylformamide (50 mL) for 30 minutes. The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide,

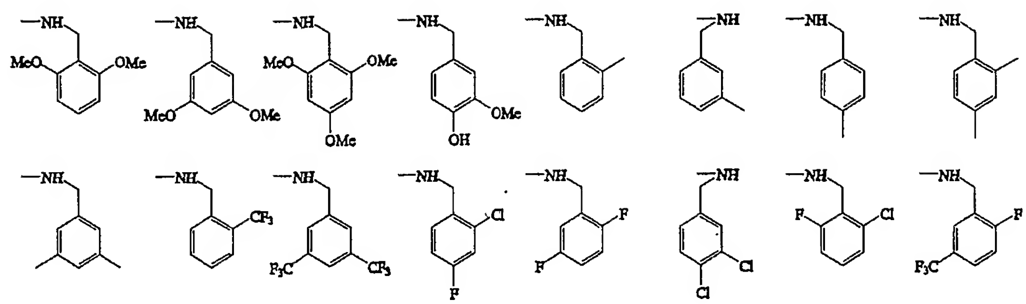
The resin was transferred to a 250 mL RBF and treated with 20 eq of 4-(phenethynyl)benzaldehyde and 40 eq of mercaptosuccinic acid in THF and heated at 60°C for 16 hours. The vessels were cooled and transferred with THF to a 250 mL peptide vessel and washed with hot THF (250 mL). The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide.

The resin was distributed into 96 wells on a parallel. synthesis apparatus (~50 mg/well). To each well was added and reacted with 20 eq. of one of 96 different amines, 20 eq. DIEA (60 μL/well), and 20 eq. diethylcyanophosphate (60 μL/well) in DCM (1 mL). The reaction was allowed to continue for 3 hours. The resin was washed exhaustively with THF, DMF, DCM, MeOH, DCM in sequence. The products were cleaved with 95% TFA/DCM for 1 hour, drained and collected into a 96 well plate. The solvent was removed under reduced pressure on a speed vac overnight. Acetonitrile (1 mL/well) was added and removed by speed vac. Ethanol (1 mL/well) was added and removed by Gene Vac. Submitted for biological assay at an estimated concentration of 8.25 μmol/well.

The various amines which were incorporated into the thiazolidinone library are displayed in Table VIII, below.

TABLE VIII .





Example 4

Example 4 sets forth a preparative synthetic route to a representative thiazolidinone of the invention, 3-[5-{[-(3,4-dichlorophenyl)ethylcarbamoyl]methyl}-4-oxo-2-(4-phenylethynylphenyl)-thiazolidin-3-yl]benzamide.

4.1 Synthesis

Into a 1000 mL RBF was added 3-aminobenzamide (3.4 g, 25 mmol), 4-phenethynylbenzaldehyde (5.2 g, 25 mmol), mercaptosuccinic acid (7.5 g, 50 mmol) and toluene (500 mL). The reaction was heated under reflux with azeotropic removal of water via a Dean-Stark trap for 8 hours. The reaction was cooled to RT, concentrated under reduced pressure, and transferred to a 2 L separatory funnel with EtOAc (500 mL). The organic phase was washed with water (2 x 1 L) and extracted with 1 N NaOH (3 x 300 mL). The combined basic extracts were washed with EtOAc (500 mL) and acidified with con. HCl. The product was then extracted with EtOAc (500 mL) and washed with saturated sodium chloride solution (2 x 500 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to leave a yellow solid. The solid was triturated with hot DCM and the resulting off-white solid was collected by filtration. The solid proved to be predominately the *trans* isomer (7 g, 15.3 mmol, 61%).

Into a 500 mL RBF was added the predominately *trans* acid (7 g, 15.3 mmol), THF (250 mL), DBU (4.5 mL, 3 eq.), and MeOH (15 mL). The reaction was heated under reflux for 24 hours. HPLC indicated equilibration to 1:5 ratio of *cis*:*trans*, an additional 2 mL of DBU was added along with 15 mL of MeOH and refluxed an additional 24 hours. HPLC indicated equilibration to 1:2 ratio of *cis*:*trans*. The reaction was cooled to RT and the solvent was removed under reduced pressure leaving a yellow syrup. The syrup was dissolved in EtOAc (125 mL) and washed with 1 N HCl (3 x

100 mL). The organic layer was concentrated under reduced pressure to leave a yellow syrup.

4.2 Purification and Resolution of Enantiomers

The syrup from 4.1, above, was dissolved in DMF (20 mL) and purified by preparative HPLC (1 mL injections, C18 column, isocratic 47% AcCN/H_2O, 30 mL/min) to give the *cis* enantiomers (2.6 g, 5.6 mmol, 38%), and the *trans* enantiomers (4 g, 8.8 mmol, 58%).

Into a 4 mL vial was added the *cis* enantiomers (46 mg, 0.1 mmol), 3,4-dichlorophenethylamine (57 mg, 0.3 mmol) in DMF (1 mL), DECP (60 μL, 0.3 mmol), and DIEA (65 μL, 0.3 mmol). The reaction was stirred at room temperature for 3 hours. HPLC analysis showed the reaction to be complete. The material was purified by preparative HPLC (1.25 mL injection, C_{18} column, isocratic 60% AcCN/H_20, 30 mL/min), collected in 50 mL centrifuge tubes, and lyophilized to give the *cis* enantiomers of 3-[5-{[2-(3,4-dichlorophenyl)ethylcarbamoyl]methyl}-4-oxo-2-(4-phenylethynylphenyl)-thiazolidin-3-yl]benzamide as a white powder (35.0 mg, 0.056 mmol, 56%).

The enantiomers can be resolved by chiral chromatography to obtain optically pure compounds. Conditions for separation varies with each compound. A preparative Chiracel OD column was used to resolve the enantiomers of AF17102 and AF17439.

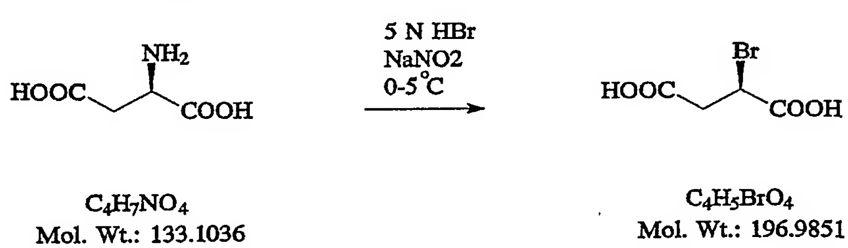
Alternatively, the individual enantiomers can be prepared synthetically by employing optically pure mercaptosuccinic acid in the thiazolidinone synthesis.

Example 5

This example details the preparation of optically pure mercaptosuccinic acid and the synthesis of optically pure thiazolidinones from this precursor.

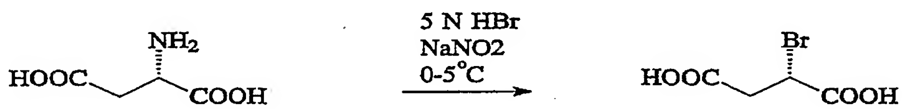
5.1 *Synthesis of optically pure mercaptosuccinic acid*

a. Preparation of (R)-Bromosuccinic acid



To a 500 mL round bottom flask was added D-aspartic acid ((R)-aspartic acid, 25 g, 188 mmol) and 245 mL of 5 N HBr. The reaction was cooled in an ice bath to 0-5°C, followed by the dropwise addition of sodium nitrite (20.7 g, 301 mmol) in 75 mL of water over five hours. The temperature was maintained below 5°C during the addition. After the addition was complete, the reaction was allowed to stir for 12 hours at 23-25°C. The reaction was diluted with diethyl ether (120 mL). The aqueous layer was removed and the organic phase was washed with 1 N HCl (100 mL). The combined aqueous phases were washed with EtOAc (100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave the product as a slightly yellow solid. The solid was recrystallized from EtOAc (~100 mL) and hexanes (~10 mL) to obtain the product (16.58 g, 84 mmol, 45%) as a white crystalline solid.

b. - Preparation of (S)-Bromosuccinic acid

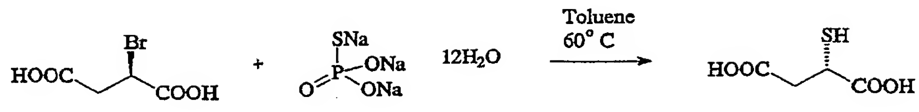


$C_4H_7NO_4$
Mol. Wt.: 133.1036

$C_4H_5BrO_4$
Mol. Wt.: 196.9851

To a 500 mL round bottom flask was added L-aspartic acid ((S)-aspartic acid, 25 g, 188 mmol) and 245 mL of 5 N HBr. The reaction was cooled in an ice bath to 0-50°C, followed by the dropwise addition of sodium nitrite (20.7 g, 301 mmol) in 75 mL of water over five hours. The temperature was maintained below 50°C during the addition. After the addition was complete, the reaction was allowed to stir for 12 hours at 23-25°C. The reaction was diluted with diethyl ether (120 mL). The aqueous layer was removed and the organic phase was washed with 1 N HCl (100 mL). The combined aqueous phases were washed with EtOAc (100 mi). The combined organic extracts were dried (MgSO4), filtered and concentrated under reduced pressure to leave the product as a slightly yellow solid. The solid was recrystallized from EtOAc (~100 mL) and hexanes (~10 mL) to obtain the product (19.03 g, 97 mmol, 51%) as a white crystalline solid.

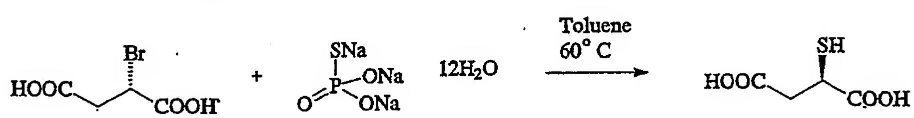
c. Preparation of (S)-Mercaptosuccinic acid.



$C_4H_5BrO_4$ Mol. Wt.: 196.9851 | $H_{24}Na_3O_{14}PS$ Form. Wt.: 396.1837 | $C_4H_6O_4S$ Mol. Wt.: 150.1490

To a suspension of sodium thiophosphate dodecahydrate (6 g, 15 mmol) in toluene (50 mL) in an oil bath at 60°C was added (R)-bromosuccinic acid (0.5 g, 2.5 mmol). The reaction was stirred at 60°C for 3.5 hours (as the reaction temperature approaches 60°C, the sodium thiophosphate melts forming a biphasic reaction medium). The toluene was then removed under reduced pressure and the resulting white solid was diluted with water (25 mL) and 1 N hydrochloric acid (30 mL), a pH of 1-1.5. The reaction was stirred at 23-25°C for 1-2 hours, then extracted with EtOAc (3x5O mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to dryness under reduced pressure. The resulting white solid was dissolved in water (3.0 mL) and filtered through a 0.2 μm nylon filter. The filtrate was purified by preparative HPLC (a single injection of 3.0 mL, a Waters PrepPak cartridge Delta-Pak C18 compression column, 15 μm 25x100 mm, 95/5 water/acetonitrile at 12.0 mL/min). The product was collected and lyophilized to afford the product (276 mg, 18.4 mmol, 72.5%) as a white solid.

d. Preparation of (R)-Mercaptosuccinic acid

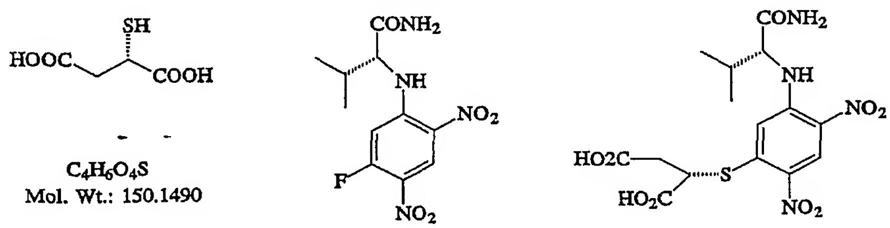


$C_4H_5BrO_4$ Mol. Wt.: 196.9851 | $H_{24}Na_3O_{14}PS$ Form. Wt.: 396.1837 | $C_4H_6O_4S$ Mol. Wt.: 150.1490

To a suspension of sodium thiophosphate dodecahydrate (6 g, 15 mmol) in toluene (50 mL) in an oil bath at 60°C was added (S)-bromosuccinic acid (0.5 g, 2.5 mmol). The reaction was stirred at 60°C for 3.5 hours (as the reaction temperature approaches 60°C, the sodium thiophosphate melts forming a biphasic reaction medium). The toluene was then removed under reduced pressure and the resulting white solid was diluted with water (25 mL) and 1 N hydrochloric acid (30 mL), a pH of 1-1.5. The

reaction was stirred at 23-25° C for 1-2 hours, then extracted with EtOAc (3x50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to dryness under reduced pressure. The resulting white solid was dissolved in water (3.0 mL) and filtered through a 0.2 µm nylon filter. The filtrate was purified by preparative HPLC (a single injection of 3.0 mL, a Waters PrepPak cartridge Delta-Pak C18 compression column, 15 µm 25x100 mm, 95/5 water/acetonitrile at 12.0 ml/min). The product was collected and lyophilized to afford the product (280 mg, 18.7 mmol, 73.5%) as a white solid.

e. Determination of Enantiomeric Excess (%ee)



To a 1 wt% solution of N^{α}-(2,4-dinitrofluorophenyl)-L-valinamide in acetone (2.0 ml) is added mercaptosuccinic acid (2.0 mg) and 0.5 M $NaHCO_3$ (1.0 ml). The reaction mixture is heated to 57°C for 45 minutes. The mixture is removed and diluted with 0.5 N $NaHCO_3$ (5.0 mL), and washed with ethyl acetate (10 mL). The aqueous phase is acidified with 1 N HCl and extracted with ethyl acetate (5 mL). The adduct is then analyzed by HPLC.

5.2 *Synthesis of optically pure thiazolidinones*

The synthesis of optically pure thiazolidinones from the optically pure precursor, mercaptosuccinic acid proceeds as outlined in Scheme 1.

To a 100 mL peptide vessel was added 2.0 g of Argogel-Rink Amide-FMOC (0.33 mmol/g loading). The resin was washed with dichloromethane (50 mL) and N,N-dimethylformamide (50 mL). The resin was then deprotected with 20% piperidine in N,N-dimethylformamide (50 mL) for 30 minutes. The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide. 3-Aminobenzoic acid (N-Fmoc protected, 1.0 g, 2.8 mmol) was coupled to the resin with HATU (1.16 g, 3.0 mmol) and DIEA (0.53 mL, 6.0 mmol) in DMF (12 mL) for 16 hours. The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide. The resin was then deprotected with 20% piperidine in N,N-dimethylformamide (50 mL) for 30 minutes.

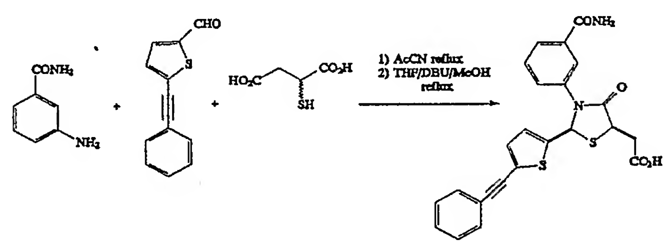
The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide.

The resin was split into 2 equal portions and each portion was treated with 10 eq of 4-benzyloxybenzaldehyde and 20 eq. of either R (70% EE) or S (75% EE) mercaptosuccinic. Acetonitrile (5 mL) was added and the reaction was left at RT for 48 hours, then 55 °C for 48 hours. The vessels were cooled and their contents were transferred with THF to a peptide vessel, and washed with hot THF. The resin was then washed exhaustively with dichloromethane and N,N-dimethylformamide.

Each portion was further reacted with 20 eq. of 3,4-dimethoxyphenethylamine, 20 eq. DIEA, and 20 eq. diethylcyanophosphate in DCM for three hours. The resin was washed exhaustively with THF, DMF, DCM, MeOH, DCM in sequence. The products were cleaved with 95% TFA/DCM for 1 hour, drained and washed with DCM (2 x 2 mL). The solvent was removed under reduced pressure leaving a yellow solid which was purified by preparative HPLC. R-Mercaptosuccinic acid afforded the *cis* isomer (18 mg, as a 96:4 mixture of 2S,5R:2S,5S). S-Mercaptosuccinic acid afforded the *cis* isomer (4 mg, as a 55:45 mixture of 2R,5S:2S,5R) and *trans* isomer (20 mg, as a 55:45 mixture of 2S,5S:2R,5R). The enantiomeric purity was determined on a Pirkle Leucine column employing 65% THF/35% hexane as the eluent at 0.7 ml/min.

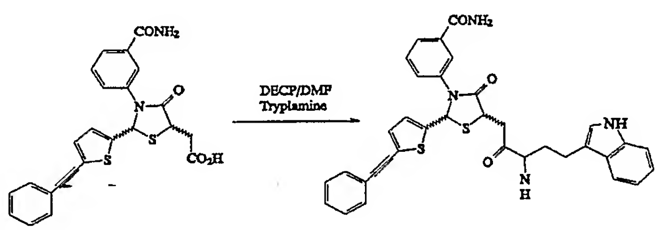
<u>Example 6</u>

This example details the synthesis of thiophene compounds of the invention.



Into a 250 mL RBF was added 3-aminobenzamide (1-6 g, 11.8 mmol), 5-(phenethynyl)thiophene-2-carboxaldehyde (2.5 g, 11.8 mmol), mercaptosuccinic acid (5.3 g, 35.4 mmol) and acetonitrile (200 mL). The reaction was heated under reflux for 3 days. A white solid had formed. The solid was collected by filtration, and washed with acetonitrile. The solid proved to be the trans isomer (4.0 g, 8.6 mmol, 73%). The filtrate was discarded. The trans isomer was transferred to a 500 mL RBF, with 200 mL THF,

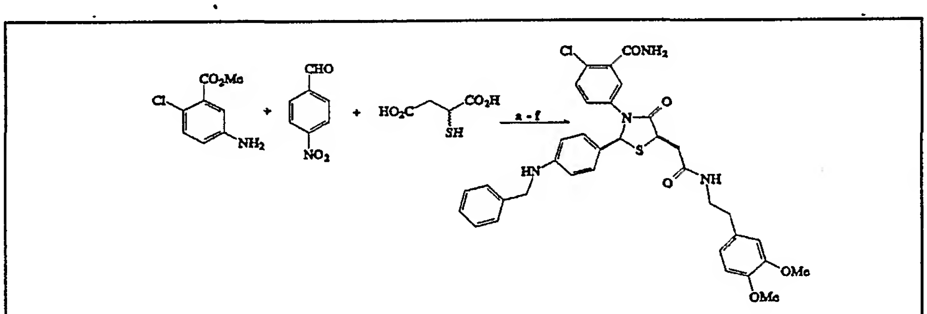
and 10 equivalents of DBU. The reaction was heated under reflux, followed by the addition of -20 mL of methanol. The reaction was reflux for 24 hours, cooled, and the solvent removed under reduced pressure. The residue was dissolved in EtOAc (250 mL) and washed with 1 N HCI (2 x 300 mL). The organic layer was filtered to remove the trans isomer, and then concentrated under reduced pressure. The remaining material was triturated with acetonitrile, filtered, and process repeated to achieve material with 95:5 cistrans ratio. This material was then recrystallized from acetonitrile to afford the cis isomer (>97:3).



Into a 2 mL vial was added the carboxylic acid (25 mg, 0.054 mmol), tryptamine (25 mg) in DMF (0.5 mL), DECP (30 µL), and DIEA (50 µL). The reaction was stirred at room temperature for 24 hours. HPLC analysis showed the reaction to be complete. The material was purified by preparative HPLC (C18 column, 5-95% AcCN/H_2O over 40 minutes, 30 mL/min) to give the cis enantiomers as a white solid (AF21639, 28.0 mg, 0.046 mtnol 86%). HPLC, MS confirm product.

Example 7

This example details the synthesis of phenethylamine compounds of the invention.

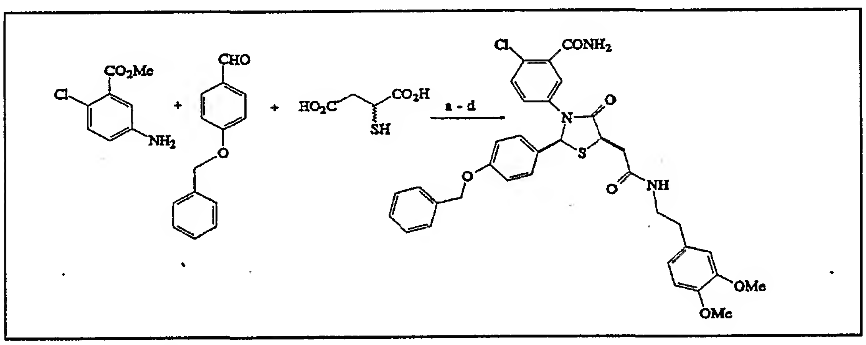


(a) AcCN/reflux; (b) DECP/DIEA/DMF/amine; (c) LiI/DMF; (d) Boc_2O/DMF/pyridine/NH_4CO_3; (e) $SnCl_2$/DMF; (f) benzaldehyde/DMF/$NaBH_3CN$.

Into a 500 mL RBF was added methyl 5-amino-2-chlorobenzoate (6.5 g, 35 mmol), 4-nitrobenzaldehyde (5.3 g, 35 mmol), mercaptosuccinic acid (15.75 g, 105 mmol), acetonitrile (250 mL). The reaction was heated under reflux for 2 days. The reaction was diluted in EtOAc (1000 mL) and washed with water (3 x 500 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to leave a yellow syrup. The syrup was dissolved in DMF (20 mL) and standard DECP coupling to 3,4-dimethoxyphenethylamine was employed. Reaction was washed, dried, and purified by flash chromatography. The resulting solid was dissolved in DMF with 3 equivalents of lithium iodide and heated at 120 °C for three days. The reaction was complete, and was washed, dried, and used directly for the Ungashe reaction. After workup, the nitro group was reduced with 3 equivalents of tindichloride in DMF. The material was washed, and reductively alkylated with benzaldehyde and sodium cyanoborohydride. The product was worked up as usual, and purified by preparative HPLC to give the product as a white powder.

Example 8

This example illustrates the synthesis of a benzyl ether derivative of the invention.



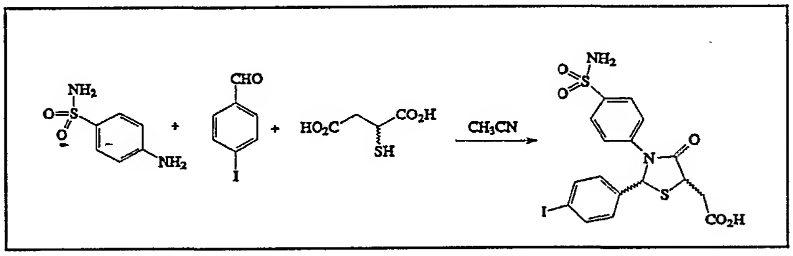
(a) AcCN, reflux; (b) DECP/DIES/DMF/amine; (c) LiI/DMF; BOC_2O/DMF/pyridine/NH_4CO_3.

Into a 500 mL RBF was added methyl 5-amino-2-chlorobenzoate (6.5 g, 35 mmol), 4-benzyloxybenzaldehyde (7.43 g, 35 mmol), mercaptosuccinic acid (15.75 g, 105 mmol), acetonitrile (250 mL). The reaction was heated under reflux for 3 days. The reaction was diluted in EtOAc (1000 mL) and washed with water (3 x 500 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to leave a yellow syrup. The syrup was dissolved in DMF (20 mL) and standard DECP

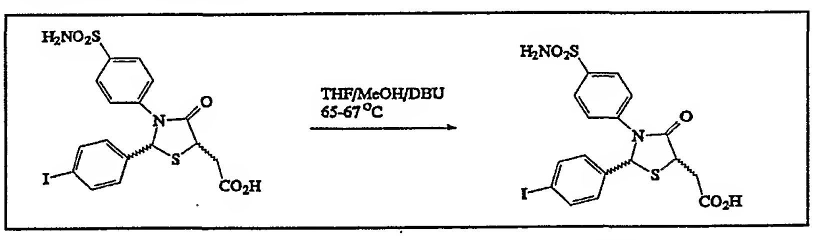
coupling to 3,4-dimethoxyphenethylamine was employed. Reaction was washed, dried, and purified by flash chromatography. The resulting solid was dissolved in DMF with 3 equivalents of lithium iodide and heated at 120 °C for three days. The reaction was complete, and was washed, dried, and used directly for the Ungashe reaction. The product was worked up as usual, and purified by preparative HPLC to give the product as a white powder.

Example 9

This example illustrates the preparation of iodobenzyl derivatives of compounds of the invention.



Into a 500 mL was added sulfanilamide (3.71 g, 21.6 mmol) 4-iodobenzaldehyde (5 g, 21.6 mmol), mercaptosuccinic acid (10 g, 64.8 mmol) and acetonitrile (300 mL). The reaction was heated under reflux for 3 days. The reaction was cooled and concentrated under reduced pressure to leave a yellow solid. The solid was dissolved in EtOAc (250 mL) and washed with 1N HCl (2 x 250 mL), water (3 x 250 mL), and saturated sodium chloride solution (1 x 100 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to leave a yellow solid. The solid was refluxed in chloroform (300 mL), filtered and dried to afford the product (10.5 g, 20.2 mmol, 93%) as a 1:8 ratio of cis:trans enantiomers. HPLC, MS, ^{1}H NMR, and ^{13}C NMR all confirm product.

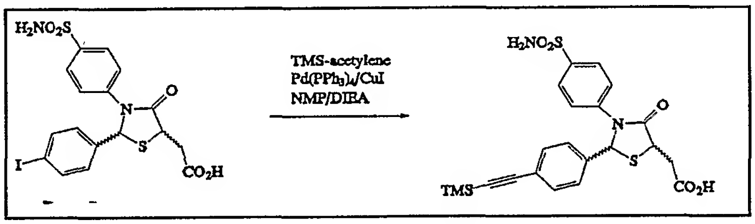


Into a 500 mL RBF was added the predominately trans acid (5.2 g, 10 mmol). THF (200 mL), DBU (15 mL), and MeOH (50 mL). The reaction was heated under reflux for 48 hours. The reaction was cooled to RT and the solvent was removed

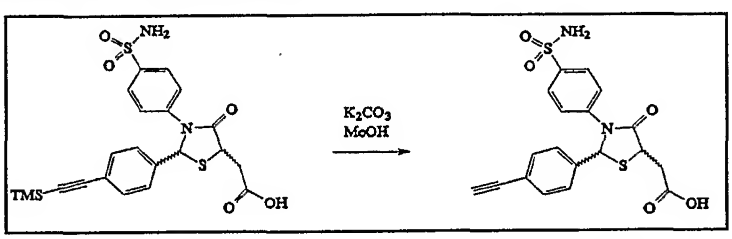
under reduced pressure leaving a yellow syrup. The syrup was dissolved in EtOAc (250 mL) and washed with 1N HCl (3 x 250 mL). The organic layer was concentrated under reduced pregsure to leave a yellow solid. The solid was refluxed in chloroform (300 mL), filtered and dried to afford the product (2.25 g, 4.3 mmol, 43%) as a 2;3 ratio of cis:trans enantiomers. HPLC, MS, ^{1}H NMR, and ^{13}C NMR all confirm product.

Example 10

This example illustrates the exchange of acetylene for iodine in the compound of Example 9.



Into a 100 mL 3-necked RBF was added the predominately trans acid (5.2 g, 10 mmol), NMP (75 mL), DIEA (51 mmol), and trimethylsilylacetylene (51 mmol). The reaction was deoxygenated by alternating application of vacuum and nitrogen. Tetrakis(triphenylphosphine)palladium(0) (1.156 g, 1 mmol) and copper(I)iodide (760 mg, 4 mmol) were added and the reaction was again deoxygenated. The reaction was stirred under nitrogen at RT for 20 hours. The reaction was diluted with EtOAc (250 mL) and washed with 1N HCl (3 x 250 mL). The organic layer was concentrated under reduced pressure to leave an orange syrup. The syrup was triturated with $CHCl_3$ (100 mL) to precipitate the product (3.4 g, 7.0 mmol, 70%) as an off-white solid. HPLC, MS, ^{1}H NMR, and ^{13}C NMR all confirm product.

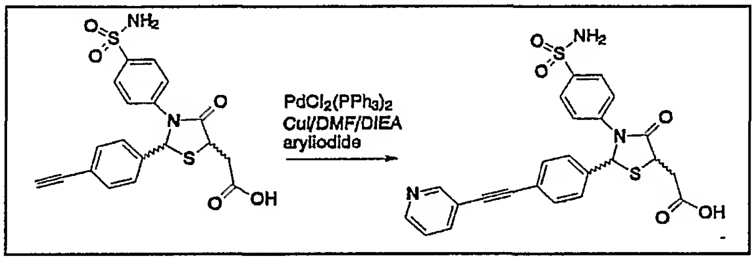


Into a 200 mL RBF containing the carboxylic acid (3.4 g, 7 mmol) was added methanol (100 mL) and potassium carbonate (10 g, 70 mmol). The reaction mixture was stirred at RT for 4 hours. The reaction mixture was diluted with EtOAc (200 mL) and washed with ^{1}N HCl (3 x 500 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to leave a yellow syrup. The

syrup was dissolved in DMF (6 mL) and purified by preparative HPLC (2 mL injection, C18 column 50% AcCN/H_2O, 30 mL/min) to give the product (2.4 g, 5.8 mmol, 82%) as a 1:2 mixture of cis:trans isomers. HPLC, MS both confirm product.

Example 11

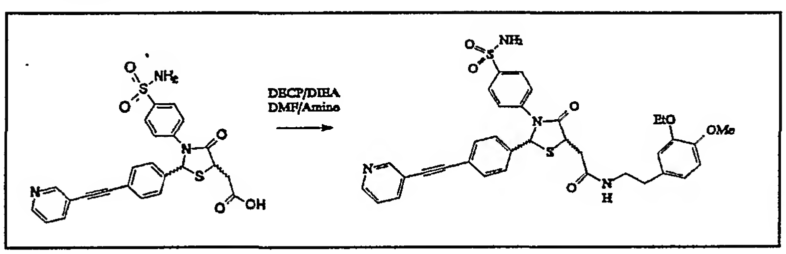
This example illustrates the coupling of pyridine to the acetyline moiety of the compound of example 10.



Into an 8 mL vial was added the carboxylic acid (250 mg, 0.6 mmol), 3-iodopyridine (200 mg), dichlorobis (triphertylphosphine)palladium(II) (45 mg, 0.06 mmol), copper(I) iodide (49 mg, 0.26 mmol), NMP (4 mL) and DIEA (0.44 mL). The reaction was stirred at RT for 24 hours. The reaction mixture was filtered through a 0.2 micron PTFE filter and purified by preparative HPLC (2 mL injections, C18 column, 5-95% AcCN/H_20 over 60 minutes, 30 mL/min) to give the product (225 mg, 0.46 mmol, 76%) as a white solid. HPLC, MS, ^{1}H NMR, ^{13}C NMR all confirm product.

Example 12

This example illustrates the derivatization of the carboxylic acid moiety of the compound of Example 11 with an amine.

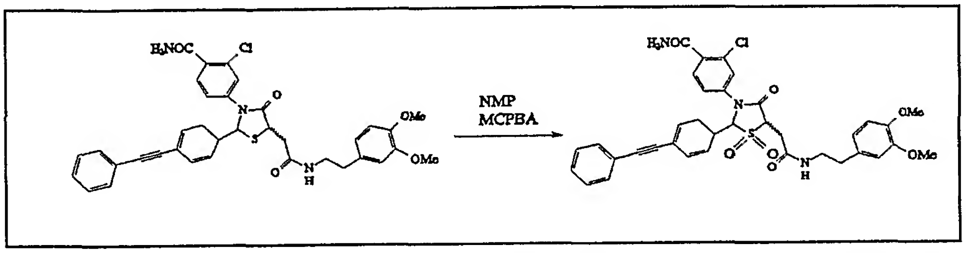


Into a 20 mL vial was added the carboxylic acid (225 mg, 0.46 mmol), 3-ethoxy-4-methoxyphenethylamine (102 µL, 0.55 mmol) in DMF (4 mL), DECP (90 µL, 0.55 mmol), and DIEA (240 µL, 0.55 mmol). The reaction was stirred at room temperature for 24 hours. HPLC analysis showed the reaction to be complete. The material was purified by preparative HPLC (2.25 mL injections, C18 column, isocratic

35% AcCN/H_2O, 30 mL/min) to give the cis enantiomers as a slightly yellow powder (AP20645, 61.9 mg, 0.092 mmol, 20%). HPLC, MS confirm product.

Example 13

This example illustrates the oxidation of the ring sulfur of a thiazolidinone compound of the invention.



Into a 4 mL vial was added the carboxylic acid (25 mg, 0.038 mmol), NMP (1 mL), and meta-chloroperbenzoic acid (46 mg). The reaction was heated at 60°C for 24 hours. The material was purified by preparative HPLC (C18 column, 5% to 95% AcCN/H_2O over 40 minutes, 30 mL/min) to give the cis:trans enantiomersas a 1:1 mixture as a white powder (AF19470,12,2 mg, 0.0178 mmol, 47%). HPLC, MS confirm product.

Example 14

This example details the protocols utilized to assay the thiazolidinone library compounds for FSH agonist activity.

a. *Testing compounds for agonist activity using a cell-based reporter assay*

Binding of FSH to the FSH receptor results in an increase in intracellular cAMP. Increases in cAMP can be monitored by the use of reporter constructs (George, SE, Bungay, PJ and Naylor, LH, "Functional coupling of endogenous serotonin and calcitonin receptor in CHO cells to a cAMP responsive luciferase reporter gene," *J. Neurochem.* 69 1278-1285 (1997), the teachings of which are incorporated herein by reference), in which the firefly luciferase gene is placed under CRE control. The human FSH receptor gene was cotransfected into CHO cells with a CRE-luciferase vector and cells expressing the FSH receptor were sorted by FACS as described above for the binding assay. Individual clones were examined for their ability to produce luciferase in response to stimulation with 1 μM FSH. Clone 1D7, which produces a response of 20-40,000 cps against a basal level of about 1,000 cps, was chosen for testing of compounds. This clone responded to FSH with an EC_{50} of about 80 pM.

Compounds were mixed with CHO FSH-R CRE-luciferase cells (100,000 cells per well in a 96 well plate) in DMEM/F12 without phenol red and incubated at 37°C for 4-6 hours. An equal volume of LucLite (Packard) was added and the plates were counted in a TopCount (Packard).

Example 15

This example illustrates the procedure utilized to test whether the thiazolidinone compounds of the invention competed with FSH for binding to the FSH receptor.

a. *Testing compounds for inhibition of binding of ^{125}I FSH to the human FSH receptor expressed on the surface of CHO cells*

The human FSH receptor was cloned into the α-T8-12CA5-KH expression vector (Koller, *et al.*, "A generic method for the production of cell lines expressing high levels of transmembrane receptors," *Analytical Biochem.* **250**:51-60 (1997), which is incorporated herein by reference), and transfected into CHO cells. After G418 selection, cells were stained with FITC-labeled 12CA5 antibody and those expressing the FSH receptor were collected by FACS. Individual clones were expanded and examined for binding of ^{125}I labeled FSH. CHO FSH-R clone 1H6 was expanded in a 15 liter spinner and membranes were prepared as described (Koller, *et al.*, *Analytical Biochem.* **250** 51-60 (1997)).

Individual compounds were examined for their inhibition of ^{125}I FSH binding to these membranes as follows:

Mix:

- 50 μl membranes diluted in binding buffer (10 mM Tris pH 7.2, 1 mM $MgCl_2$, 1 mM $CaCl_7$ containing 0.1% BSA)--use amount of membranes to generate a 10:1 signal:noise
- 25 μl sample or buffer containing 4 μM unlabeled FSH (Cortex Biochem.)
- 25 μl ^{125}I FSH (30,000 cpm per well)

Incubate for 2 hours at room temperature and filter onto pretreated GF/B Unifilter plates (blocked with 0.1% PEI for 30 minutes). Dry filter at 37°C, add 40 μl of Microscent 20 (Packard) and count using Packard TopCount.

b. *Results*

Membranes were prepared from chinese hamster ovary (CHO) cells which expressed FSH-R as described above. These cells specifically bind ^{125}I-labeled FSH. When a binding assay was performed in the presence of 100 μM thiazolidinone, no inhibition of the radiolabeled FSH was observed. Thus, although the thiazolidinones are able to bind to the FSH receptor and to elicit a response, they do not block the interaction between FSH and its receptor.

Example 16

This example illustrates a general procedure for library production by parallel synthesis on Rink Amide resin.

Step 1: Deprotection of Fmoc from Rink Amide Resin

Rink Amide Resin (loading: 0.53 mmol/g; 2.4g, 1.272mmol) was treated with a solution of 20% piperidine in DMF (2 x 25 ml, 10 min for the first time and 20 min for the second time) to remove the Fmoc protecting group from the resin. The mixture was filtered and the resin was washed with DMF (3 x 25 ml), MeOH (3 x 25ml), and CH_2Cl_2 (3 x 25ml).

Step 2: Attachment of Various Fmoc-Protected Amino Acids to the Resin

The resin (1.272 mmol) was swollen in anhydrous DMF (10 ml). A solution of Fmoc-protected amino acid (2eq., 2.544 mmol), HOBT (389.2mg, 2.544 mmol) and HBTU (964.2mg, 2.544 mmol) in anhydrous DMF (15 ml) was added to the resin followed by adding DIEA (886.3μl, 5.088 mol). The mixture was shaked at room temperature on an orbital shaker overnight. The mixture was filtered and the resin was washed with DMF (3 x 25 ml), MeOH (3 x 25ml), CH_2Cl_2 (3 x 25ml), and dried.

Step 3: Deprotection of Fmoc Group

The resin (1.272 mmol), prepared as described in step 2 above, was again treated with a solution of 20% piperidine in DMF (2 x 25 ml, 10 min for the first time and 20 min for the second time) to remove the Fmoc protecting group. The mixture was filtered and the resin was washed with DMF (3 x 25 ml), MeOH (3 x 25ml), and CH_2Cl_2 (3 x 25ml).

Step 4: Reaction with Various Aldehydes

The resin prepared above was distributed into a number of scintillation vials according to the number of different aldehydes to be used. To each amino acid on

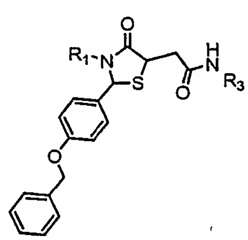
Rink Amide Resin (0.424 mmol) was added a solution of 10eq. of aldehyde (4.24mmol) and 20eq. of mercaptosuccinic acid (1.27g, 8.48mmol) in anhydrous THF (10 ml). The resulting reaction mixture was heated at 60°C on the J-KEM block for 48 hr, the mixture was filtered, washed with THF (3 x 10ml), MeOH (3 x 10ml), and CH_2Cl_2 (3 x 10ml).

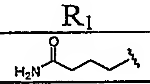
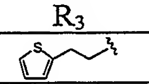
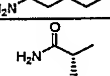
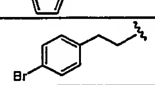
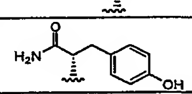
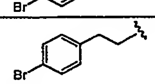
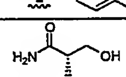
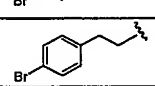
Step 5: Reaction with Various Amines

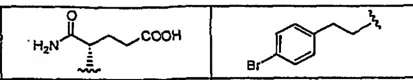
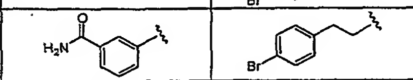
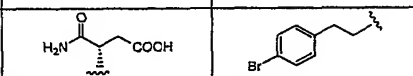
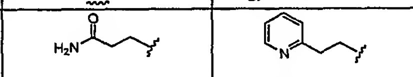
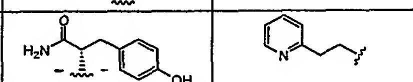
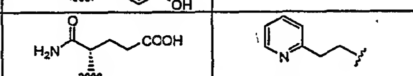
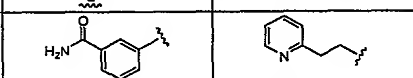
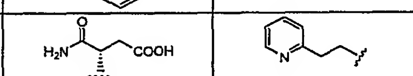
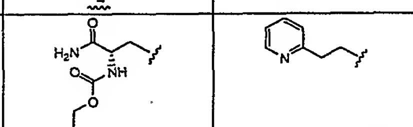
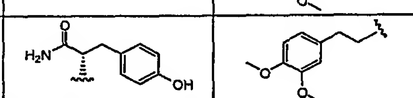
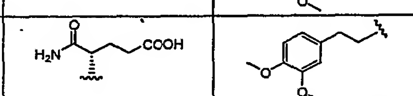
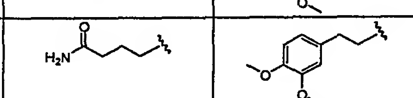
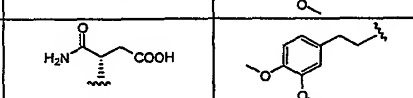
The resin again was distributed into 48 or 96 wells on a Robbins apparatus depending on the number of different amines to be used. To the resin-bound acid (0.027 mmol) was added a solution of HOBT (16.52mg, 0.108 mmol) and HBTU (41mg, 0.108 mmol) in anhydrous DMF (2 ml). DIEA(37.6µl, 0.216mmol) was then added into each well followed by 10eq. of amines(0.27mmol). The reaction mixture was rotated at room temperature on an orbital shaker overnight. The mixture was then filtered and the resin was washed with DMF (3 x 2 ml), MeOH (3 x 2ml), CH_2Cl_2 (3 x 2ml), and dried.

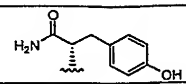
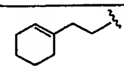
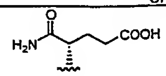
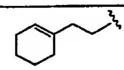
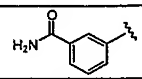
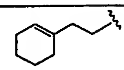
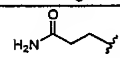
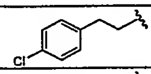
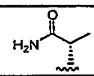
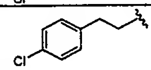
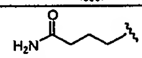
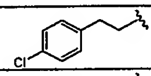
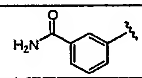
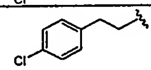
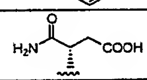
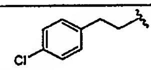
Step 6: Cleavage from the Solid Support

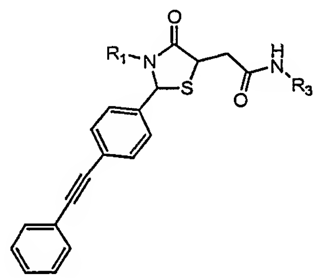
The products were cleaved from the solid support for characterization according to the following procedure. To each well was added 95% TFA/DCM (2 ml). The resin was left standing for 1 h, and the solution were filtered into a 48 or 96 wells Robbins microtiter plate. The resin in each well was washed with dichloromethane (2 ml). The solutions were concentrated under a nitrogen stream and dried in Savant under vacuum. The compounds were purified by Gilson prep HPLC and the required fractions were concentrated in Savant. The final product was characterized by LC/MS. The structure for the libraries generated are shown in the following Table.

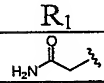
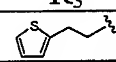
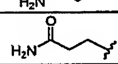
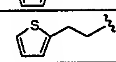
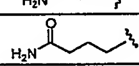
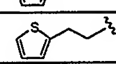
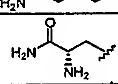
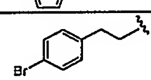
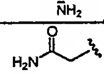
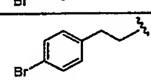
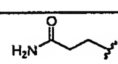
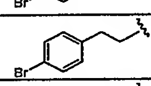
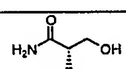
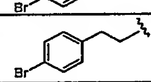
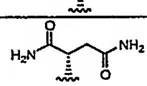
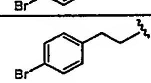
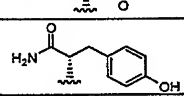
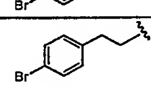
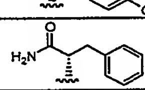
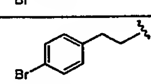
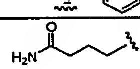
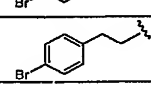


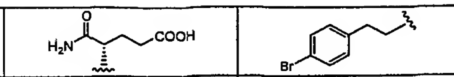
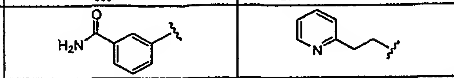
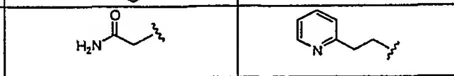
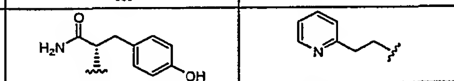
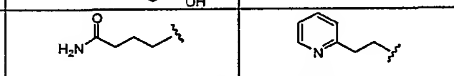
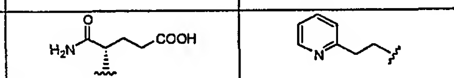
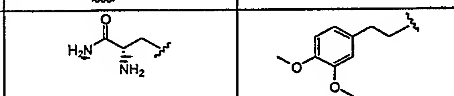
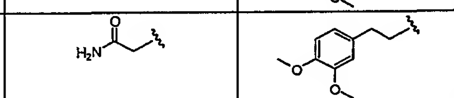
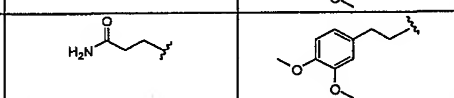
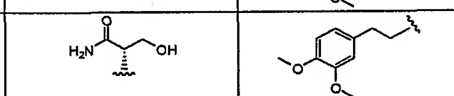
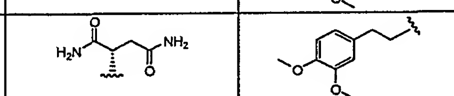
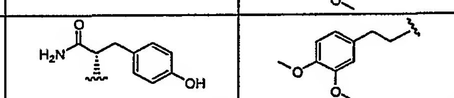
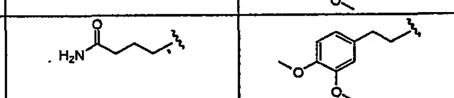
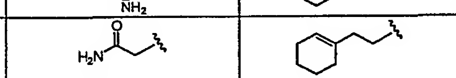
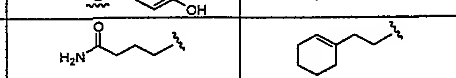
Example 16	R_1	R_3	LC@220	$(M+H)^+$
A1			5.04 min	538
B1			5.59 min	596
C1			5.51 min 5.61 min	688
D1			5.35 min	612

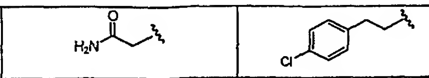
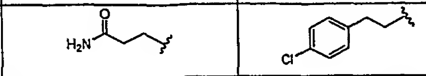
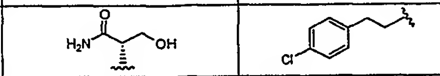
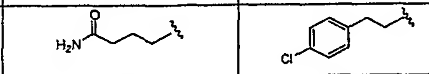
E1			5.29 min 5.35 min	654
F1			5.13 min	639
G1			5.44 min	610
H1			5.62 min	644
I1			5.42 min 5.54 min	582
J1			5.27 min	640
K1			3.78 min 3.93 min	519
L1			3.92 min 4.01 min	519
M1			4.02 min 4.11 min	611
N1			4.30 min	577
O1			4.03 min 4.14 min	567
P1			4.24 min	563
Q1			3.98 min 4.08 min	606
R1			4.99 min	578
S1			5.06 min	670
T1			4.77 min 4.81 min	636
U1			4.85 min 4.91 min	592
V1			5.01 min 5.09 min	626
W1			4.69 min 4.85 min	622
X1			4.61 min	522
Y1			4.86 min 5.12 min	598

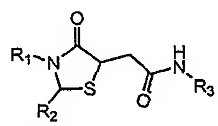
Z1			4.46 min 4.65 min	614
A2			4.29 min 4.49 min	580
B2			4.56 min 4.71 min	570
C2			5.33 min	552
D2			5.53 min	552
E2			5.38 min	566
F2			5.56 min	600
G2			5.18 min	596

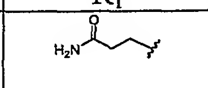
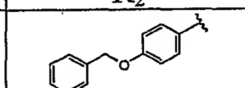
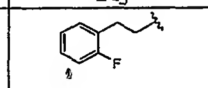
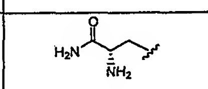
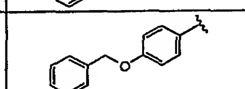
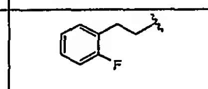
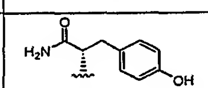
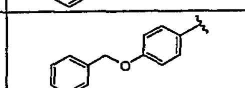
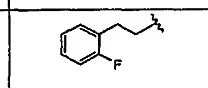
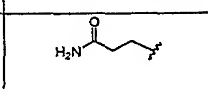
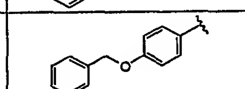
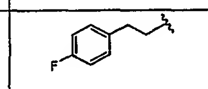
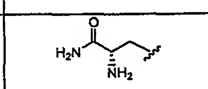
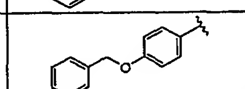
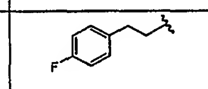
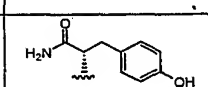
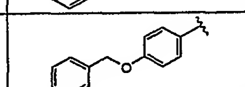
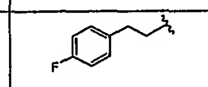
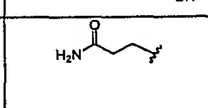
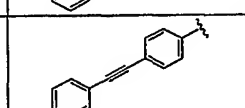
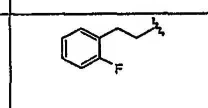
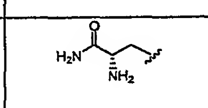
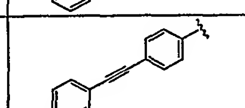
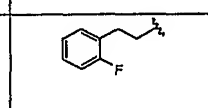
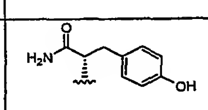
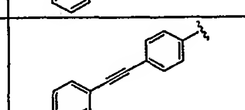
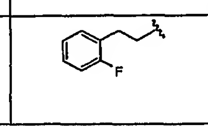


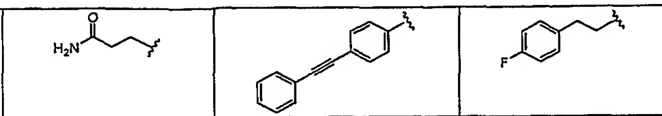
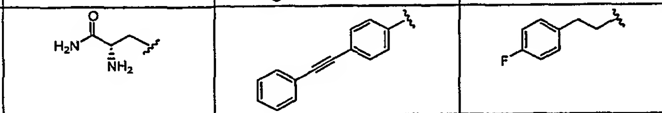
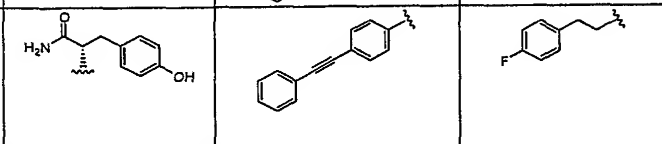
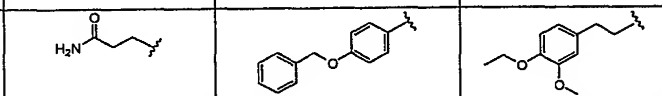
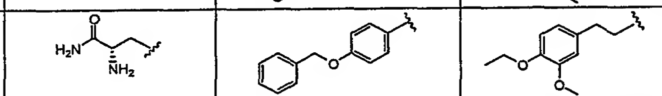
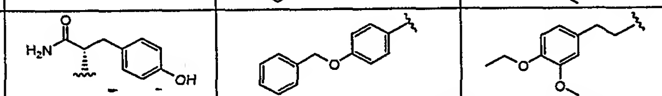
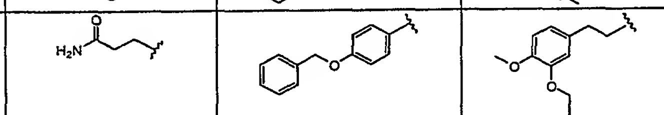
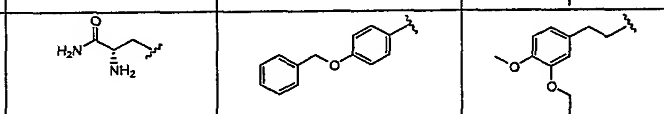
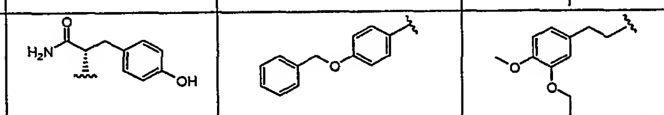
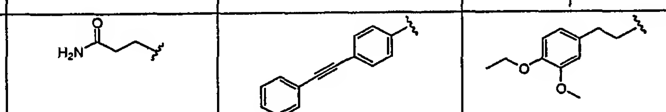
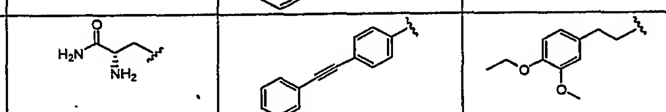
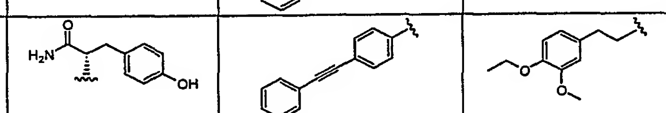
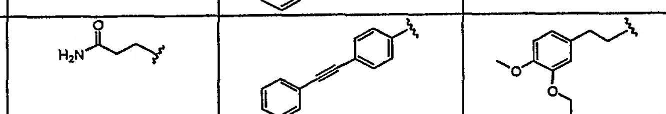
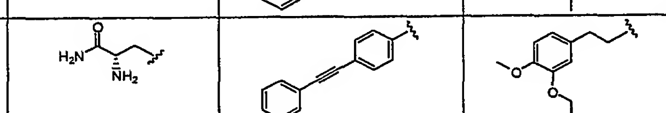
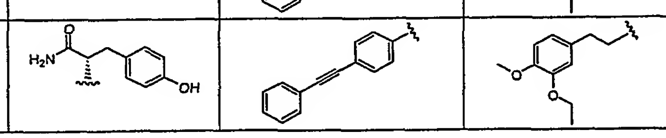
Example 16	R_1	R_3	LC@220	$(M+H)^+$
H2			5.39 min	504
I2			5.36 min	518
J2			5.42 min	532
K2			5.10 min 5.12 min	605
L2			5.78 min 5.94 min	576
M2			5.75 min	590
N2			5.74 min	606
O2			5.50 min 5.57 min	633
P2			5.90 min 6.01 min	682
Q2			6.47 min 6.63 min	666
R2			5.84 min	604

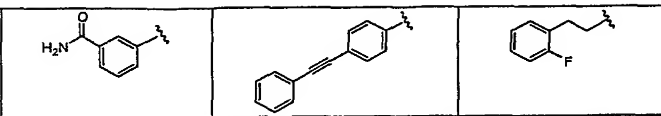
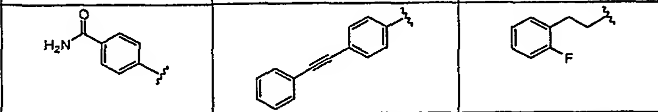
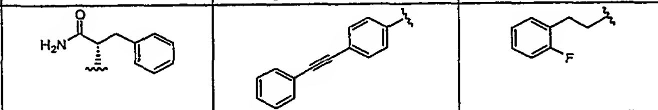
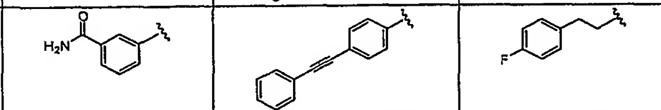
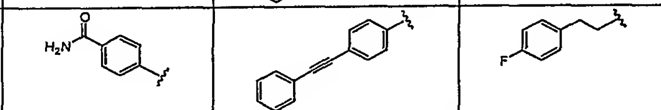
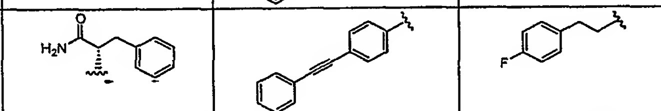
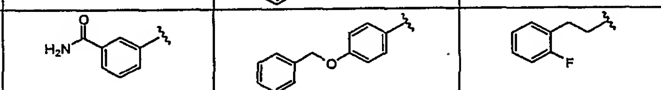
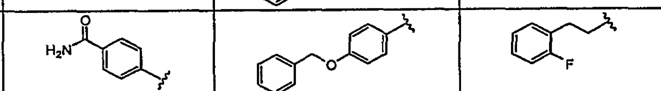
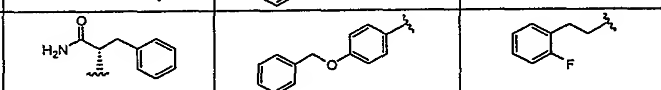
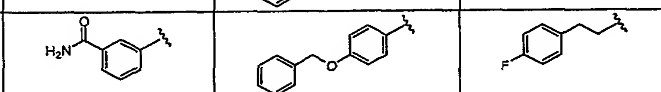
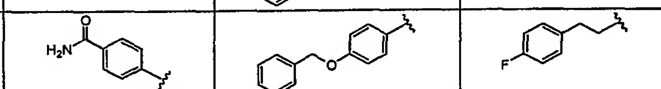
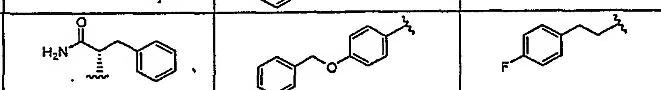
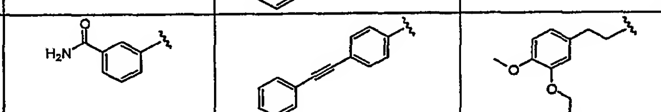
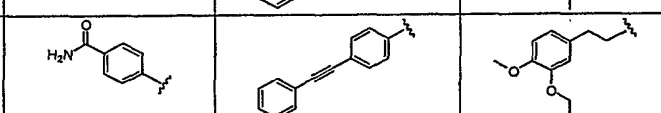
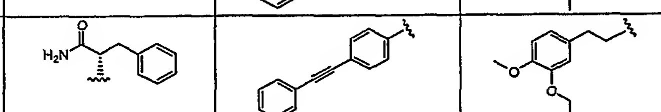
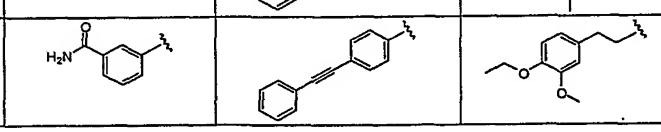
S2		5.68 min	648
T2		4.33 min 4.45 min	561
U2		4.14 min 4.30 min	499
V2		4.11 min 4.27 min	513
W2		4.15 min	529
X2		4.42 min	605
Y2		4.19 min 4.32 min	527
Z2		4.11 min 4.19 min	571
A3		4.57 min 4.71 min	587
B3		5.19 min 5.34 min	558
C3		5.13 min 5.22 min	572
D3		5.20 min	588
E3		4.95 min 4.99 min	615
F3		4.78 min	663
G3		5.19 min	586
H3		4.33 min	531
I3		4.82 min 5.03 min	502
J3		4.79 min	516
K3		4.79 min 5.06 min	608
L3		4.87 min 4.97 min	530
M3		4.97 min 5.06 min	561

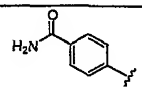
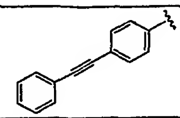
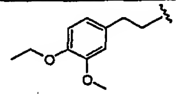
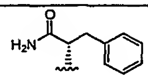
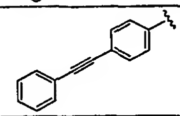
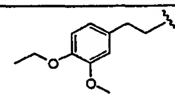
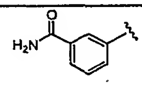
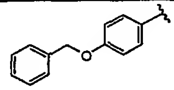
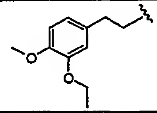
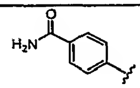
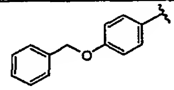
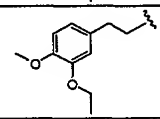
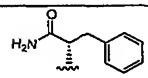
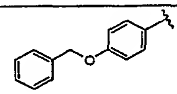
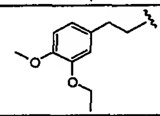
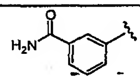
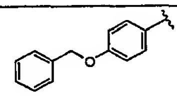
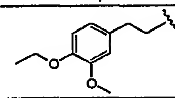
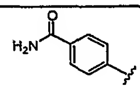
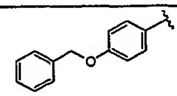
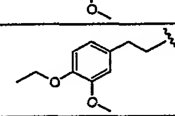
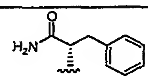
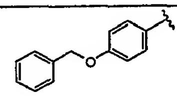
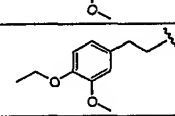
N3			5.73 min 5.91 min	532
O3			5.70 min	546
P3			5.68 min 5.78 min	562
Q3			5.75 min 5.77 min	560
R3			4.08 min 4.25 min	488
S3			4.07 min 4.22 min	502
T3			4.17 min 4.26 min	516

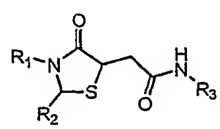


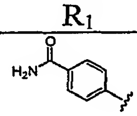
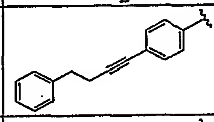
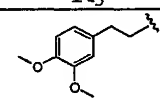
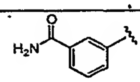
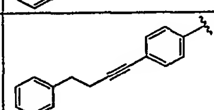
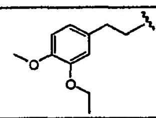
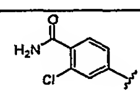
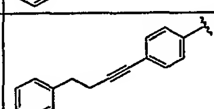
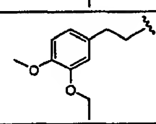
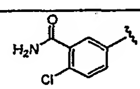
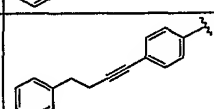
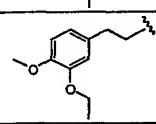
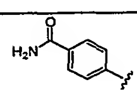
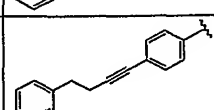
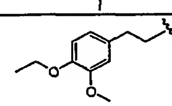
	R_1	R_2	R_3	LC@254	$(M+H)^+$
U3				2.99 min	536
V3				2.56 min 2.96 min	551
W3				3.08 min 3.13 min	628
X3				2.98 min 3.10 min	536
Y3				2.56 min 2.95 min	551
Z3				2.62 min 2.66 min	628
A4				3.14 min	530
B4				2.66 min 3.07 min	545
C4				3.24 min 3.30 min	622

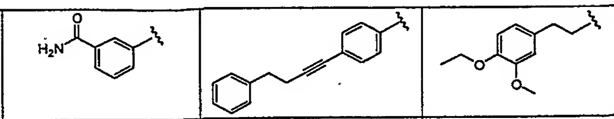
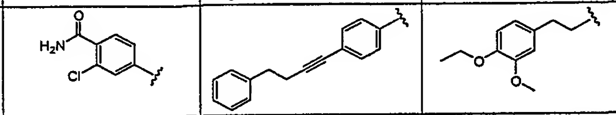
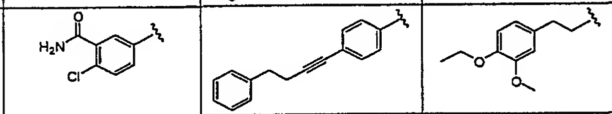
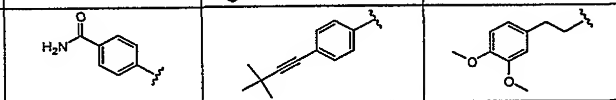
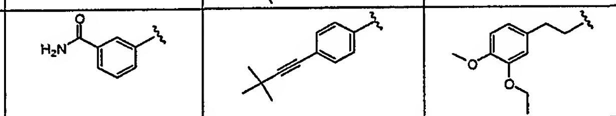
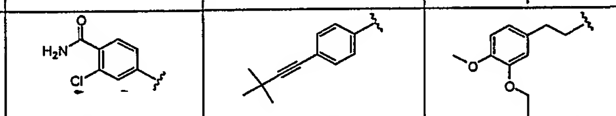
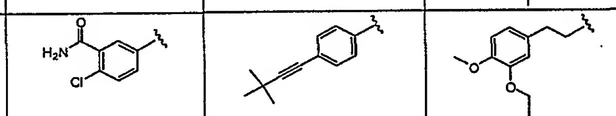
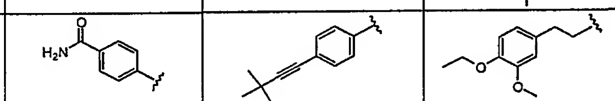
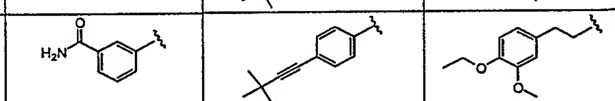
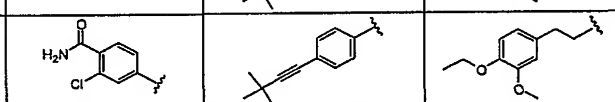
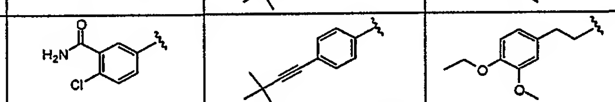
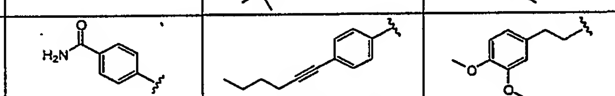
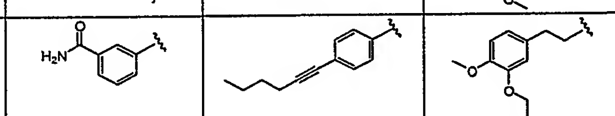
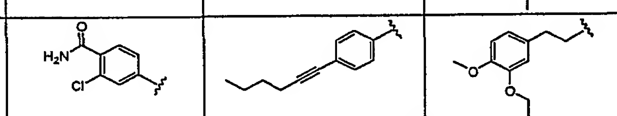
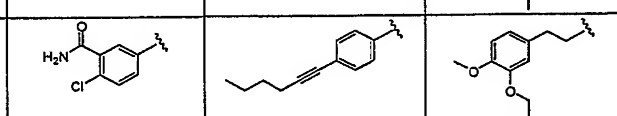
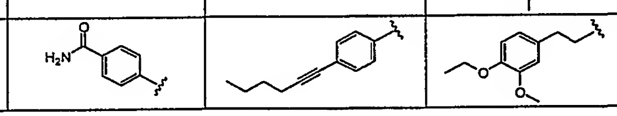
D4				3.16 min	530
E4				2.74 min 3.07 min	545
F4				3.11 min 3.24 min	622
G4				2.93 min	592
H4				2.56 min 2.95 min	607
I4					684
J4				2.96 min	592
K4				2.57 min	607
L4					684
M4					586
N4				2.45 min 2.72 min	601
O4				3.10 min	678
P4				3.10 min	586
Q4				2.65 min 2.72 min	601
R4					678

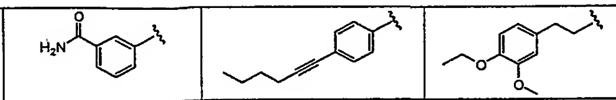
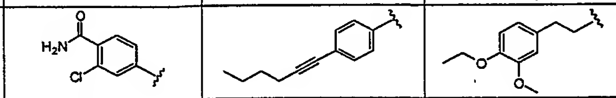
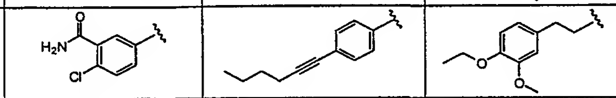
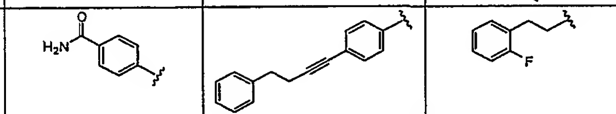
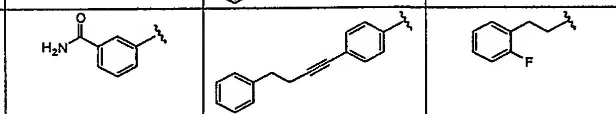
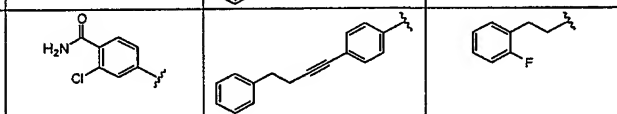
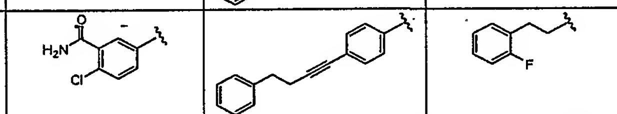
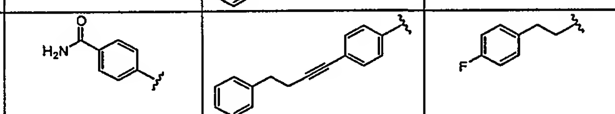
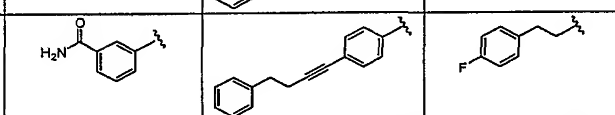
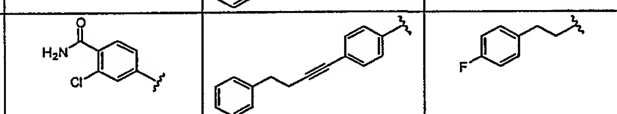
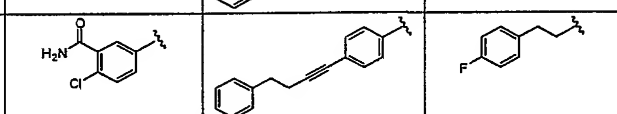
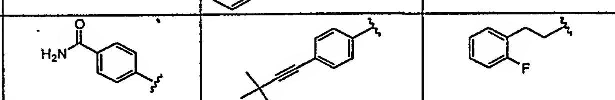
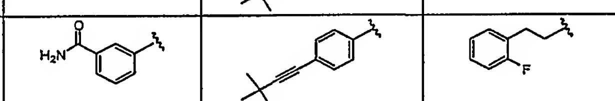
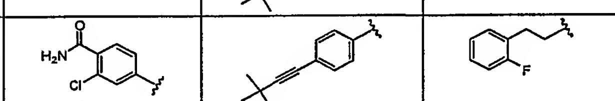
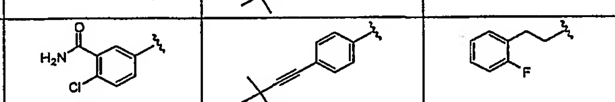
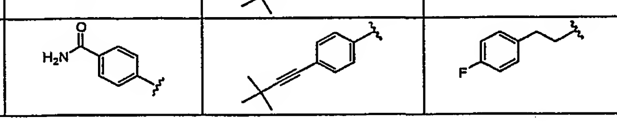
S4				4.53 min 4.65 min	578
T4				5.70 min 5.78 min	578
U4				6.27 min 6.34 min	606
V4				5.64 min 5.72 min	578
W4				5.59 min 5.67 min	578
X4				6.24 min 6.32 min	606
Y4				5.43 min	584
Z4				5.39 min	584
A5				5.85 min 5.95 min	612
B5				5.43 min	584
C5				5.38 min	584
D5				5.93 min 6.07 min	612
E5				5.50 min 5.60 min	634
F5				5.44 min 5.54 min	634
G5				6.11 min 6.27 min	662
H5				5.53 min 5.62 min	634

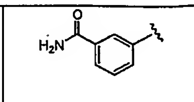
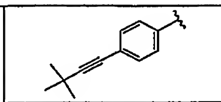
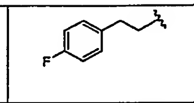
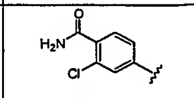
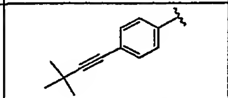
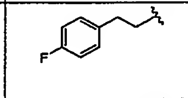
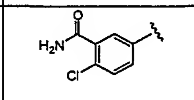
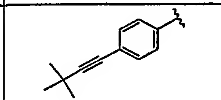
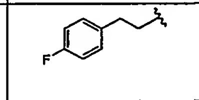
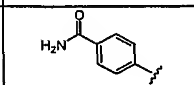
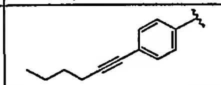
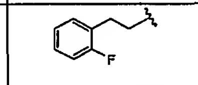
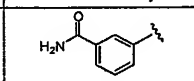
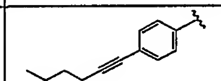
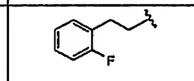
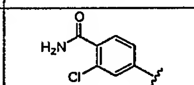
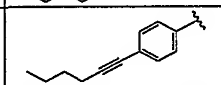
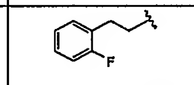
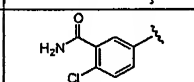
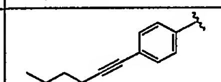
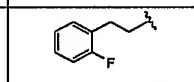
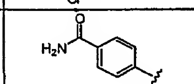
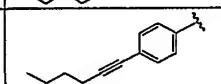
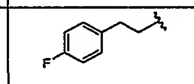
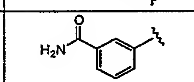
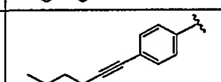
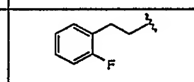
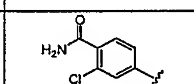
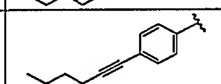
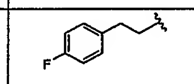
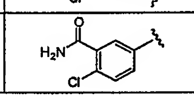
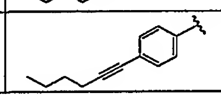
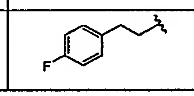
I5				5.46 min 5.56 min	634
J5				6.12 min 6.30 min	662
K5				5.23 min 5.30 min	640
L5				5.18 min 5.25 min	640
M5				5.79 min 5.92 min	668
N5				5.26 min 5.33 min	640
O5				5.21 min 5.27 min	640
P5				5.81 min 5.96 min	668

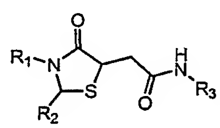


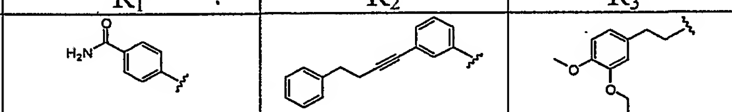
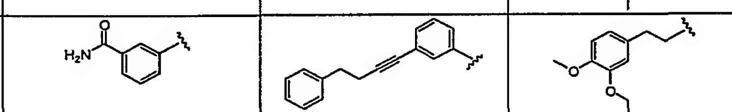
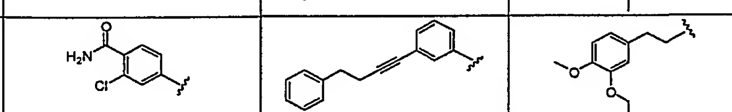
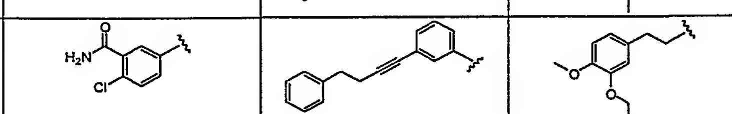
Example 16	R_1	R_2	R_3	LC@254	$(M+H)^+$
Q5				3.74 min	662
R5				3.78 min	662
S5				3.87 min 3.94 min	696
T5				3.91 min 3.98 min	696
U5				3.77 min .3.83 min	662

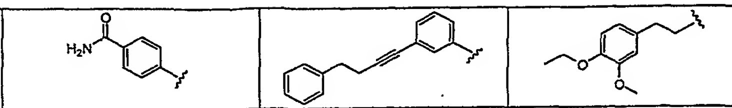
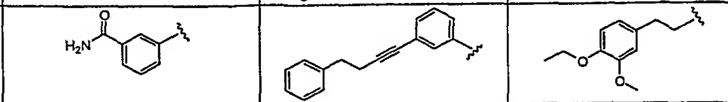
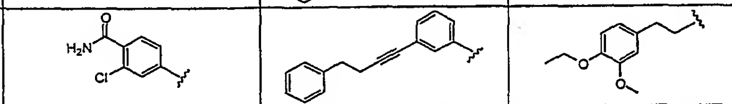
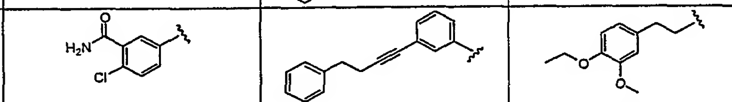
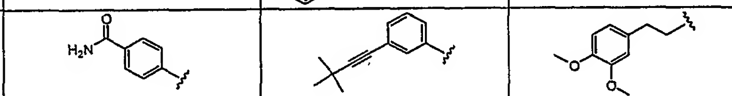
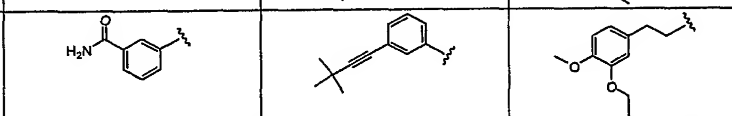
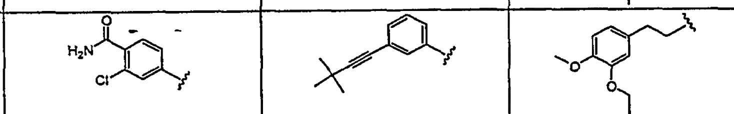
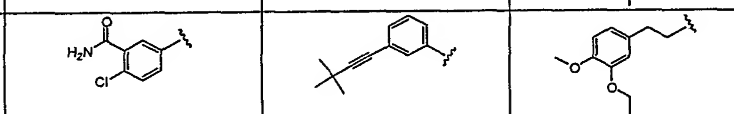
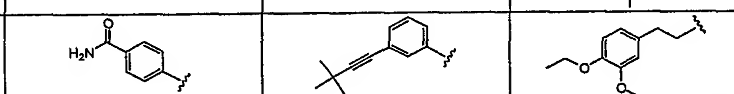
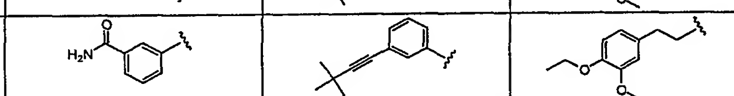
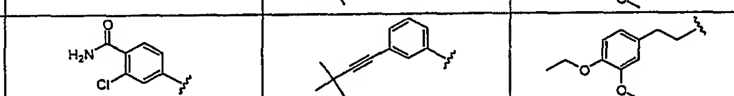
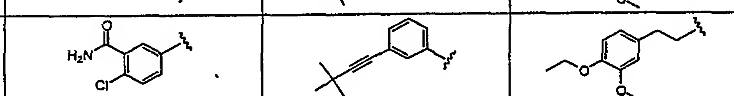
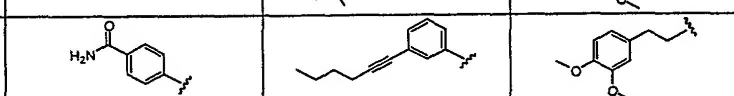
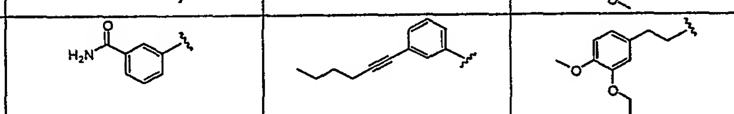
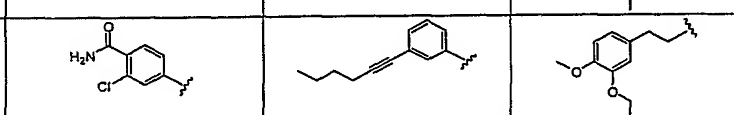
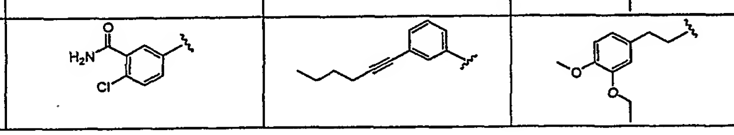
V5				3.81 min 3.88 min	662
W5				3.89 min 3.96 min	696
X5				3.93 min 3.99 min	696
Y5				3.68 min 3.75 min	614
Z5				3.72 min 3.79 min	614
A6				3.81 min 3.88 min	648
B6				3.86 min 3.93 min	648
C6				3.70 min 3.76 min	614
D6				3.74 min	614
E6				3.83 min	648
F6				3.88 min 3.94 min	648
G6				3.72 min 3.80 min	614
H6				3.77 min 3.84 min	614
I6				3.86 min 3.93 min	648
J6				3.91 min 3.98 min	648
K6				3.74 min 3.81 min	614

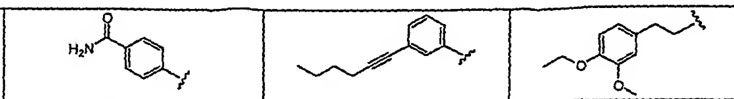
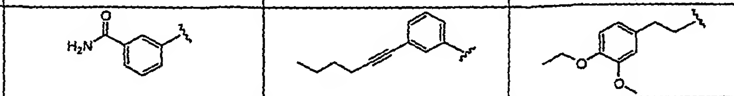
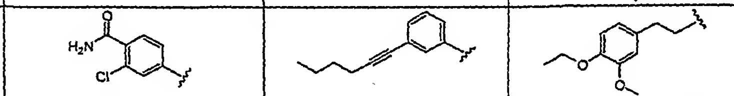
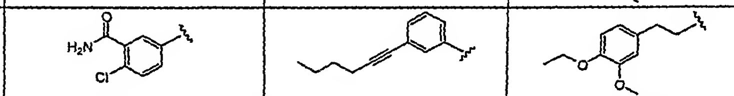
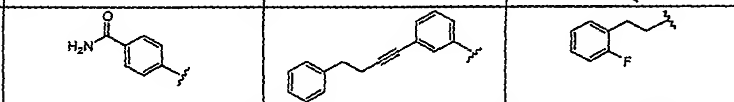
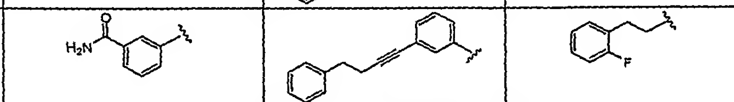
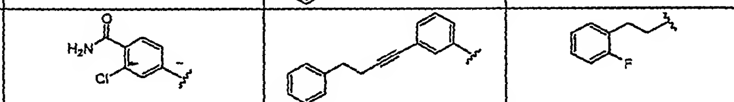
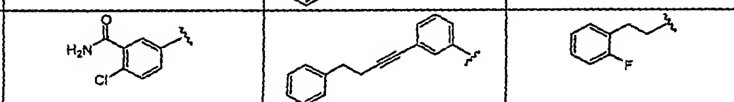
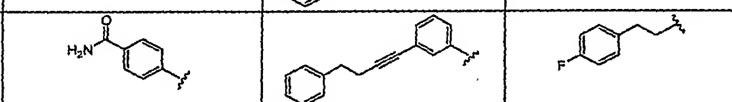
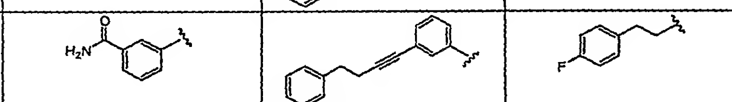
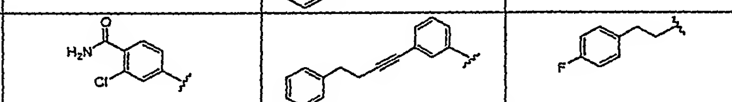
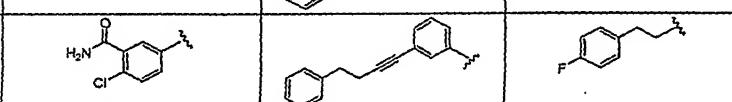
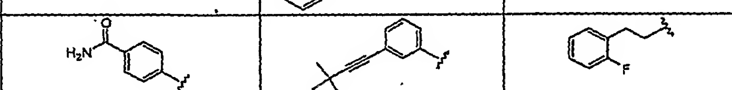
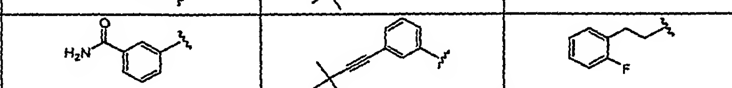
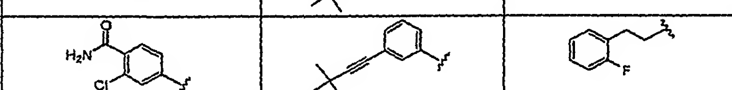
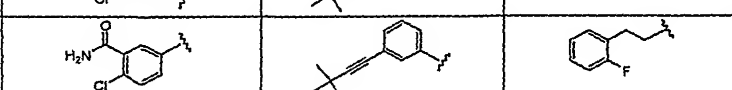
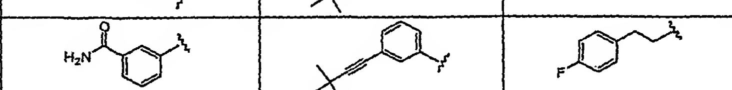
L6				3.80 min 3.86 min	614
M6				3.88 min 3.95 min	648
N6				3.92 min 3.98 min	648
O6				3.86 min	606
P6				3.90 min	606
Q6				3.99 min	640
R6				4.02 min	640
S6				3.84 min	606
T6				3.88 min	606
U6				3.97 min	640
V6				4.01 min	640
W6				3.81 min	558
X6				3.84 min	558
Y6				3.93 min 3.98 min	592
Z6				3.97 min	592
A7				3.79 min 3.84 min	558

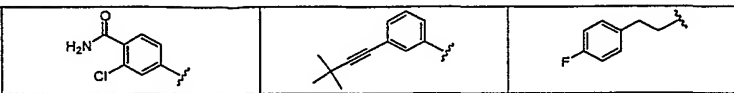
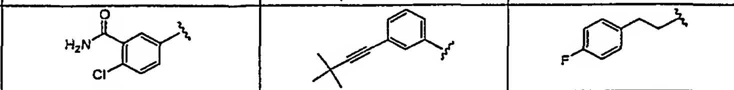
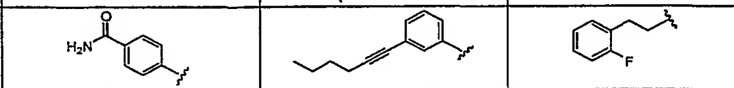
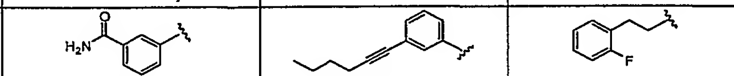
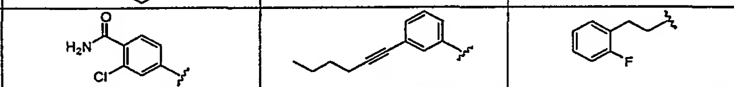
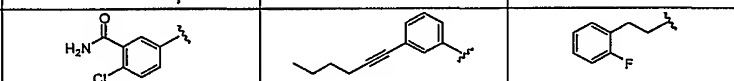
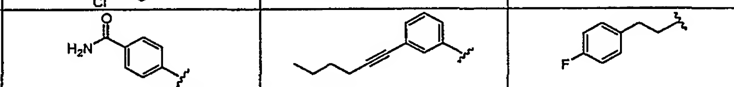
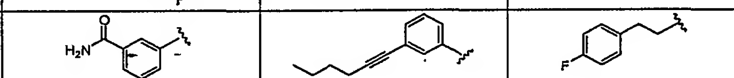
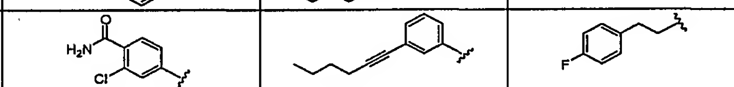
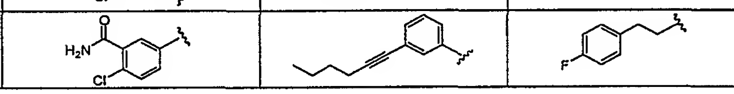
B7				3.83 min	558
C7				3.92 min 3.97 min	592
D7				3.96 min	592
E7				3.85 min	558
F7				3.89 min	558
G7				3.98 min 4.03 min	592
H7				4.02 min	592
I7				3.83 min	558
J7				3.88 min	558
K7				3.96 min 4.01 min	592
L7				4.00 min 4.05 min	592

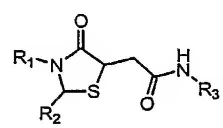


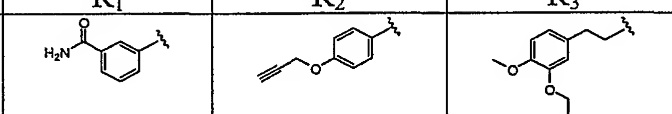
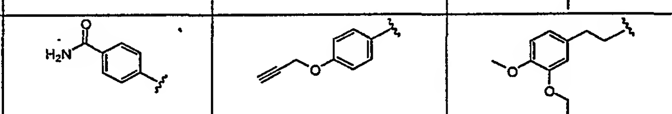
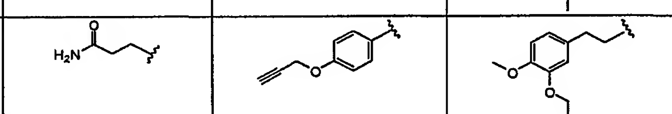
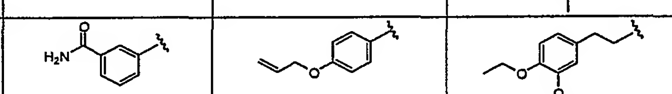
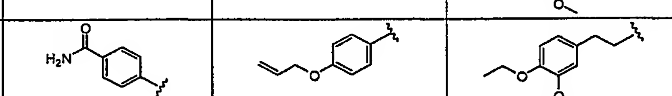
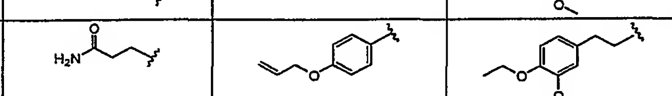
	R_1	R_2	R_3	LC@254	$(M+H)^+$
M7				3.18 min 3.24 min	662
N7				3.21 min 3.27 min	662
O7				3.27 min 3.33 min	696
P7				3.32 min	696

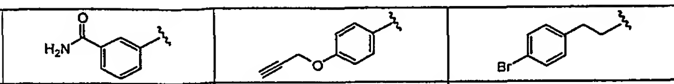
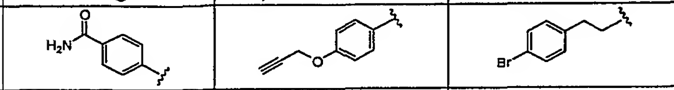
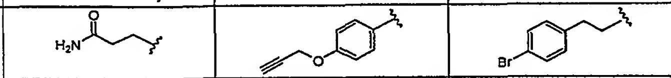
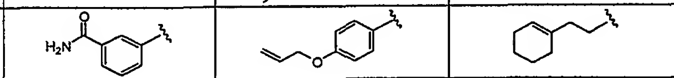
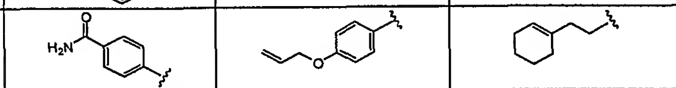
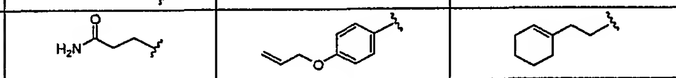
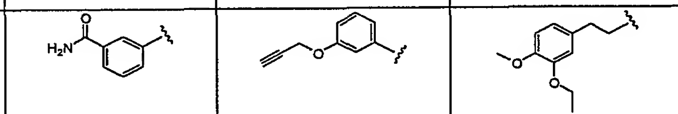
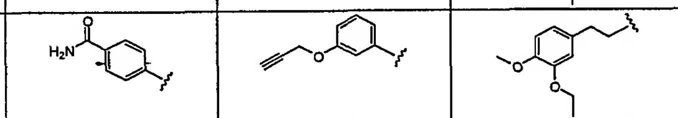
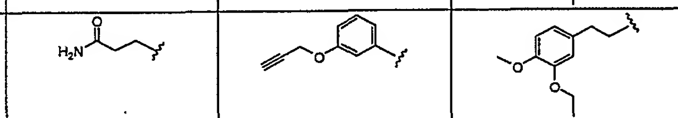
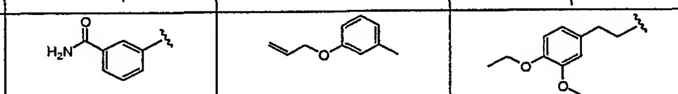
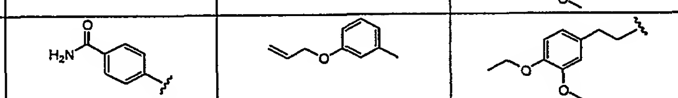
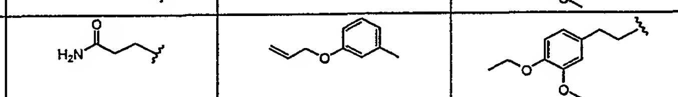
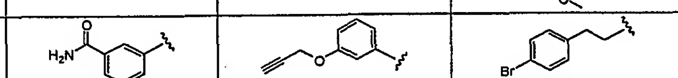
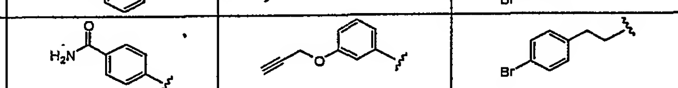
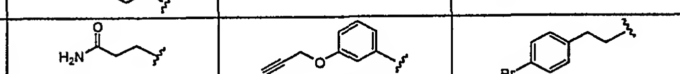
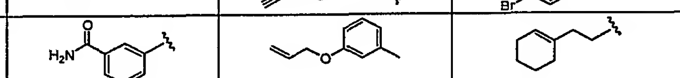
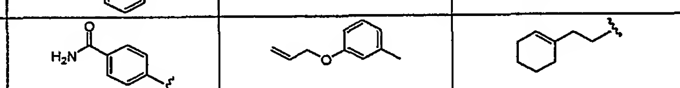
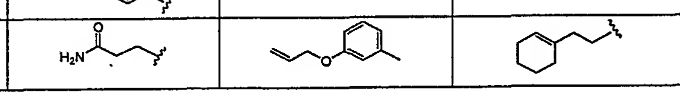
Q7				3.19 min 3.25 min	662
R7				3.23 min	662
S7				3.29 min 3.34 min	696
T7				3.33 min 3.39 min	696
U7				3.11 min 3.18 min	614
V7				3.15 min 3.22 min	614
W7				3.21 min 3.29 min	648
X7				3.26 min 3.32 min	648
Y7				3.13 min 3.19 min	614
Z7				3.17 min 3.23 min	614
A8				3.23 min 3.30 min	648
B8				3.28 min 3.33 min	648
C8				3.16 min 3.23 min	614
D8				3.19 min 3.26 min	614
E8				3.25 min 3.33 min	648
F8				3.30 min 3.37 min	648

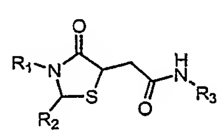
G8		3.18 min 3.24 min	614
H8		3.22 min 3.27 min	614
I8		3.27 min 3.34 min	648
J8		3.32 min 3.38 min	648
K8		3.30 min	606
L8		3.33 min	606
M8		3.38 min	640
N8		3.42 min	640
O8		3.27 min 3.30 min	606
P8		3.32 min	606
Q8		3.37 min	640
R8		3.41 min	640
S8		3.25 min	558
T8		3.28 min	558
U8		3.37 min	592
V8		3.37 min	592
W8		3.23 min	558
X8		3.27 min	558

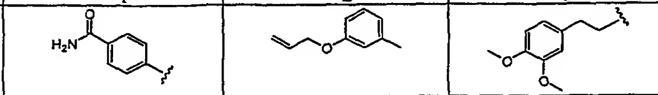
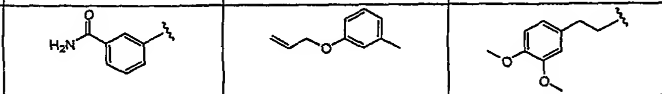
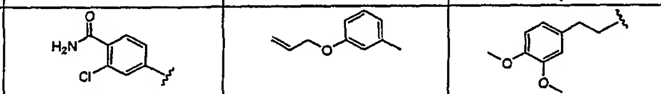
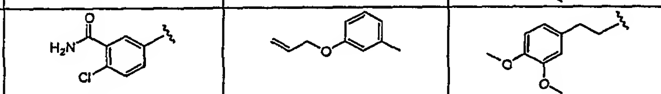
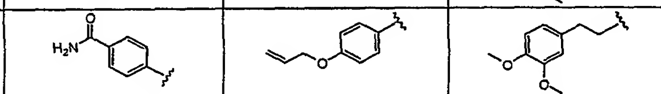
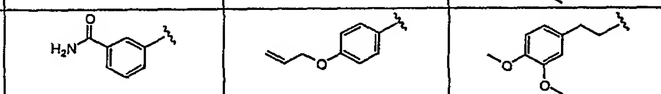
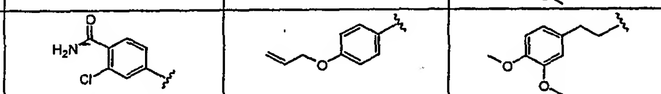
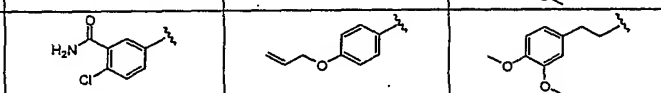
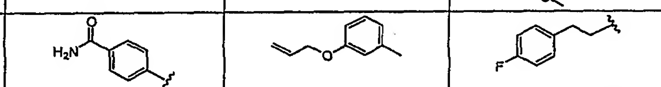
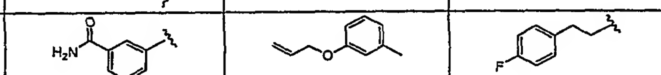
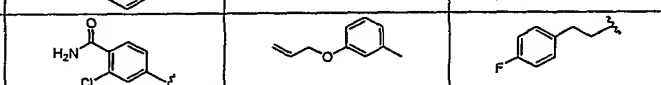
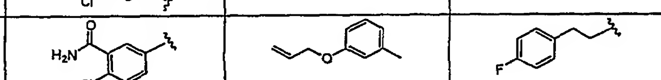
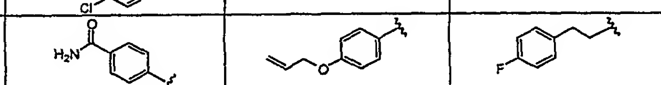
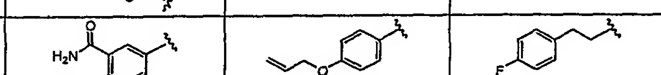
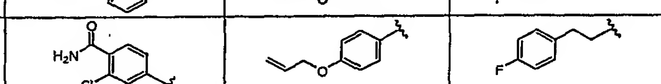
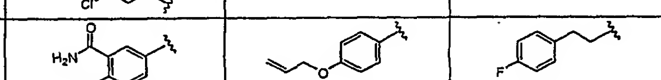
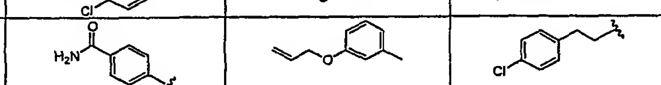
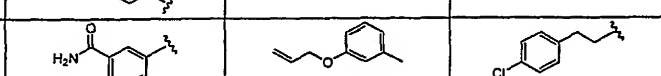
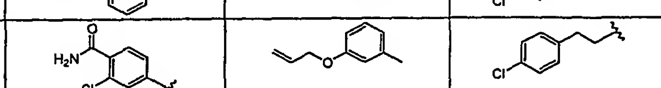
Y8				3.32 min	592
Z8				3.32 min	592
A9				3.29 min	558
B9				3.32 min	558
C9				3.38 min	592
D9				3.42 min	592
E9				3.27 min	558
F9				3.30 min	558
G9				3.39 min	592
H9				3.41	592

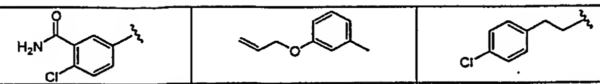
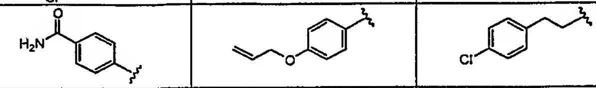
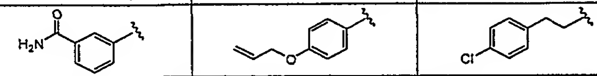
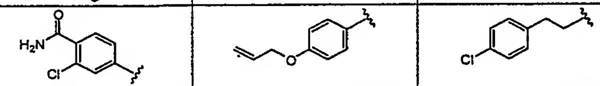
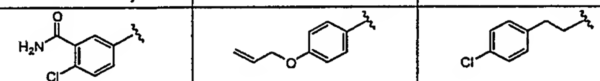
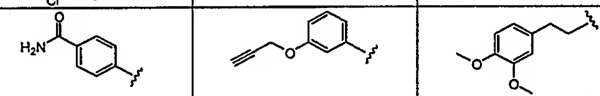
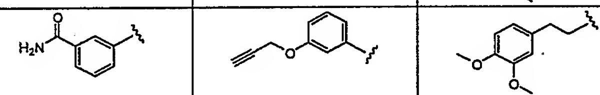
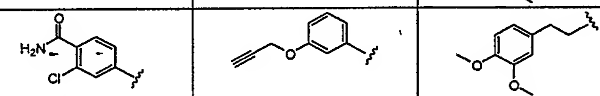
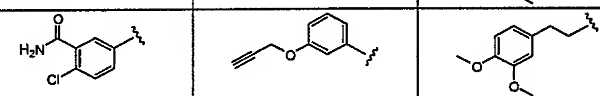
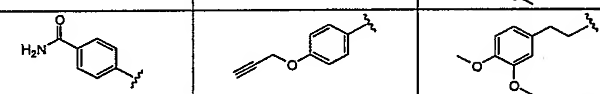
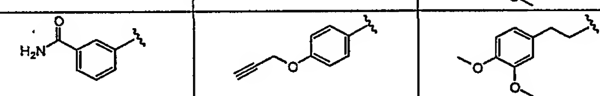
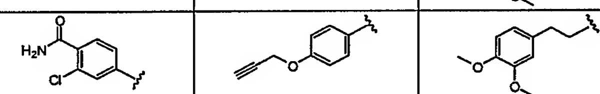
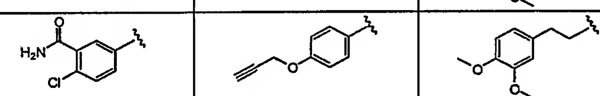
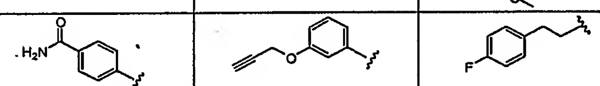
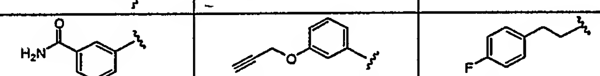
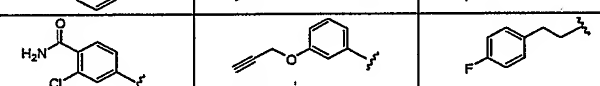
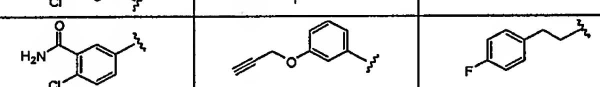
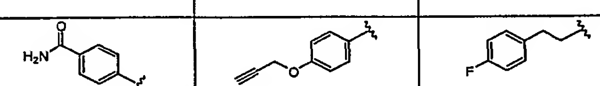
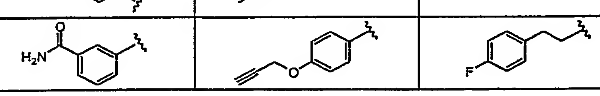


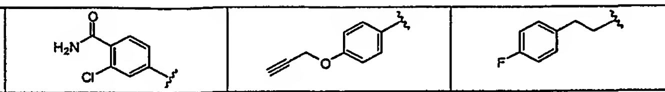
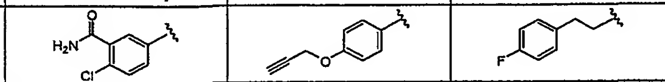
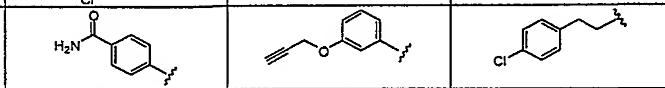
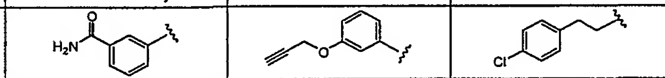
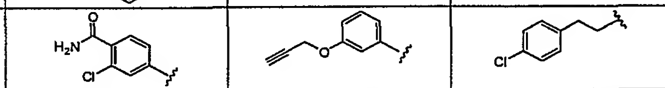
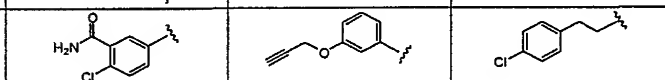
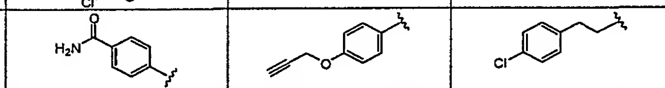
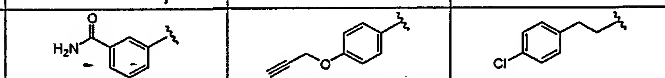
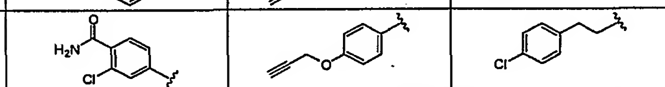
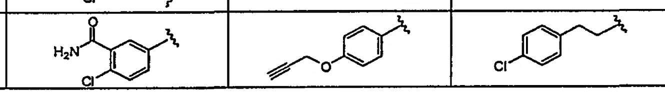
Example 16	R_1	R_2	R_3	LC@220	$(M+H)^+$
I9				2.72 min	588
J9				2.70 min	588
K9				2.57 min	540
L9				2.84 min	590
M9				2.84 min	590
N9				2.69 min	542

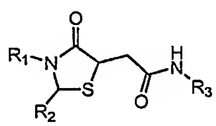
O9				2.96 min	592
P9				2.94 min	592
Q9				2.81 min	544
R9				2.41 min 2.52 min	520
S9				2.49 min	520
T9				2.41 min 2.47 min	472
U9				2.72 min	588
V9				2.70 min	588
W9				2.57 min	540
X9				2.85 min	590
Y9				2.82 min	590
Z9				2.69 min	542
A10				2.98 min	592
B10				2.96 min	592
C10				2.83 min	544
D10				2.40 min 2.52 min	520
E10				2.34 min 2.47 min	520
F10				2.40 min 2.46 min	472

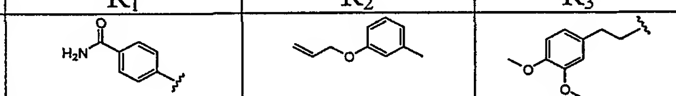
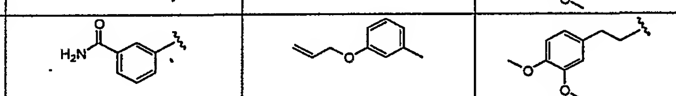
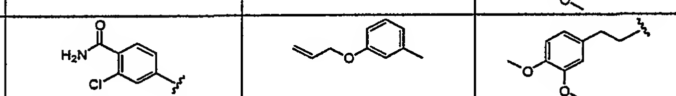
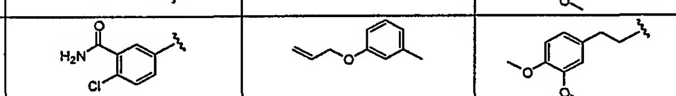
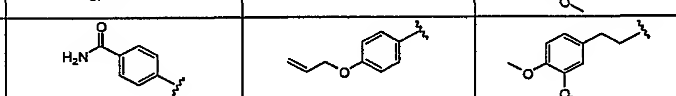
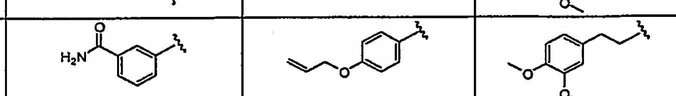
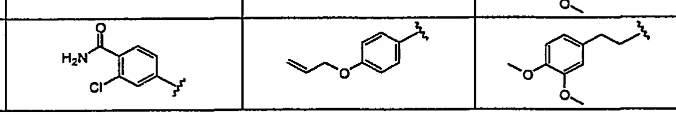


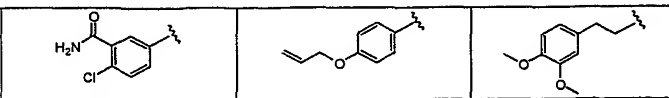
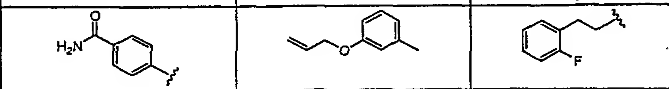
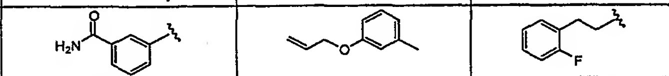
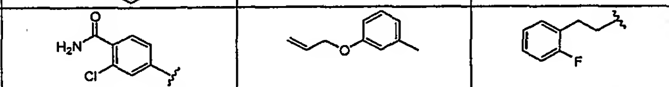
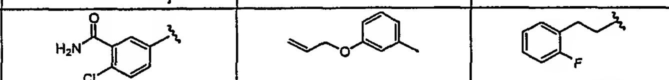
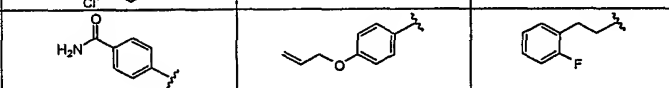
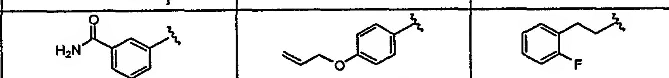
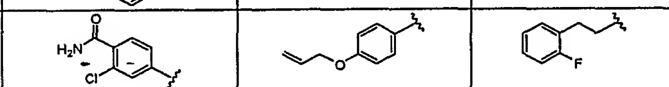
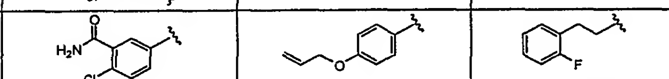
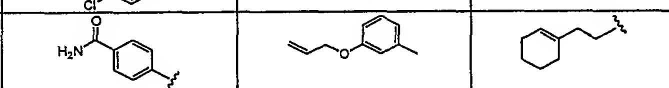
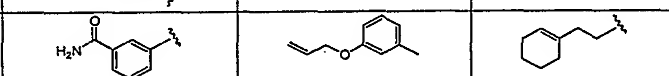
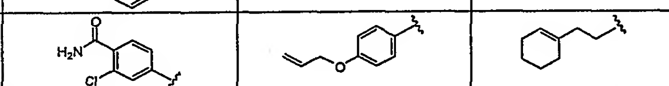
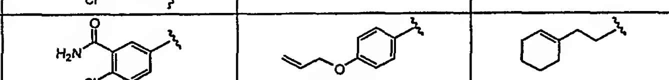
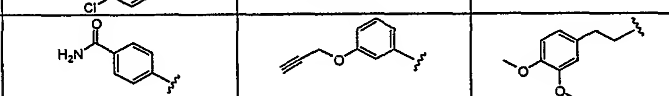
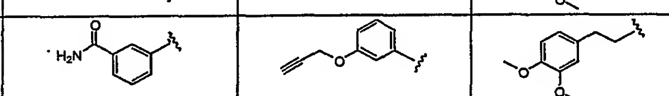
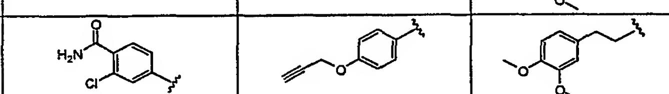
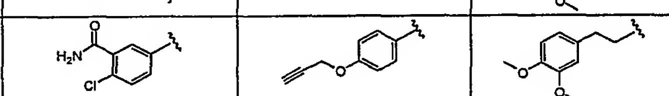
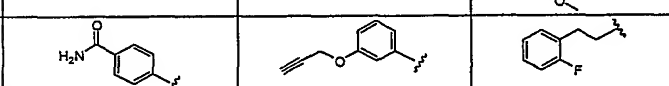
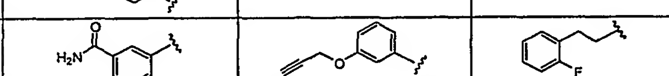
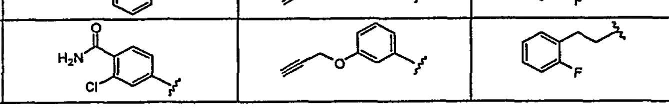
	R_1	R_2	R_3	LC@254	$(M+H)^+$
G10				3.02 min	576
H10				3.05 min	576
I10				3.17 min	610
J10				3.16 min 3.20 min	610
K10				3.02 min 3.05 min	576
L10				3.05 min	576
M10				3.13 min 3.18 min	610
N10				3.16 min 3.21 min	610
O10				3.26 min	534
P10				3.29 min	534
Q10				3.38 min	568
R10				3.41 min	568
S10				3.26 min	534
T10				3.29 min	534
U10				3.40 min	568
V10				3.40 min	568
W10				3.42 min	550
X10				3.44 min	550
Y10				3.54 min	584

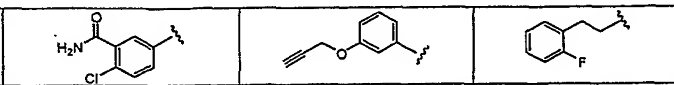
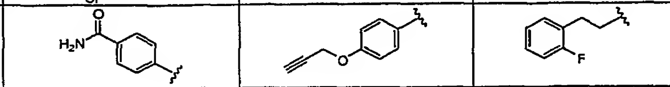
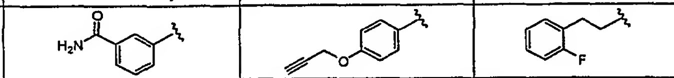
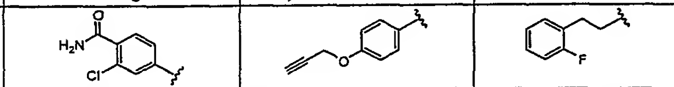
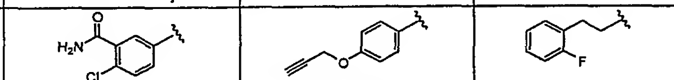
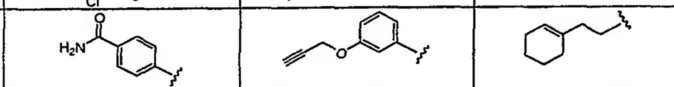
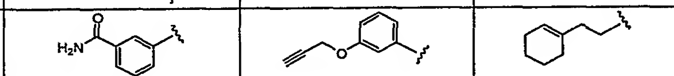
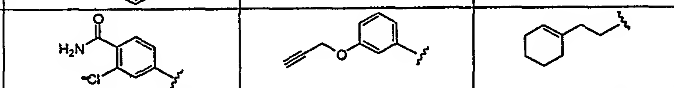
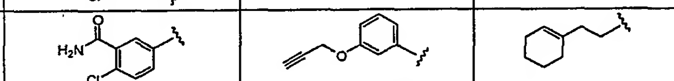
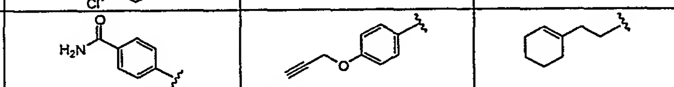
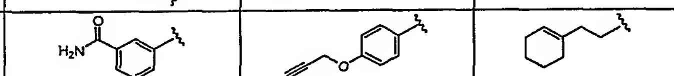
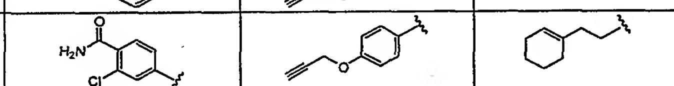
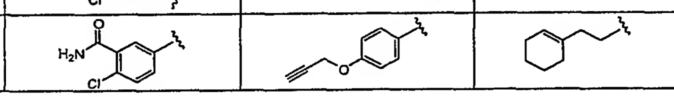
Z10				3.56 min	584
A11				3.42 min	550
B11				3.44 min	550
C11				3.55 min	584
D11				3.56 min	584
E11				2.89 min 2.93 min	574
F11				2.92 min 2.93 min	574
G11				3.00 min 3.04 min	608
H11				3.03 min 3.07 min	608
I11				2.88 min 2.92 min	574
J11				2.91 min	574
K11				3.03 min	608
L11				3.01 min	608
M11				3.14 min	532
N11				3.16 min	532
O11				3.26 min	566
P11				3.28v	566
Q11				3.13 min	532
R11				3.15 min	532

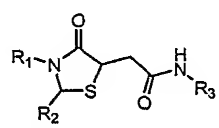
S11				3.25 min	566
T11				3.26 min	566
U11				3.30 min	548
V11				3.31 min	548
W11				3.41 min	582
X11				3.43 min	582
Y11				3.28 min	548
Z11				3.30 min	548
A12				3.40 min	582
B12				3.41 min	582

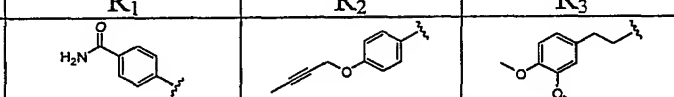
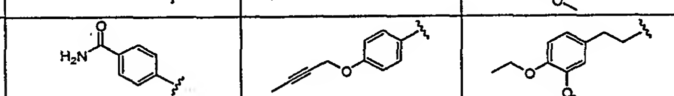
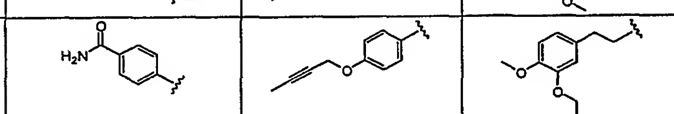
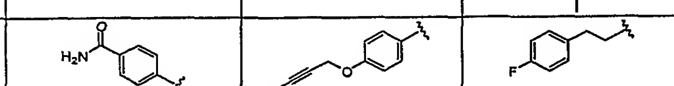


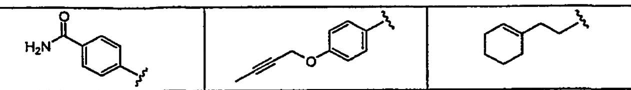
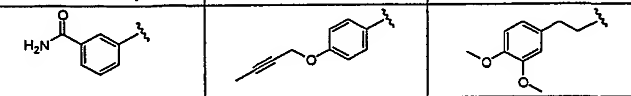
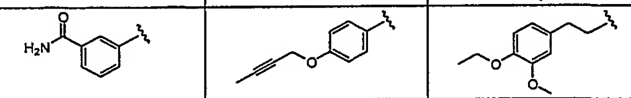
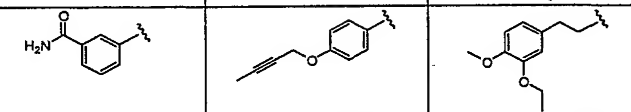
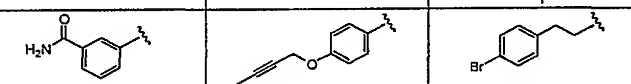
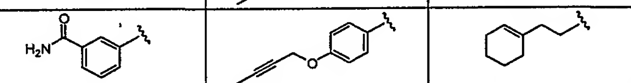
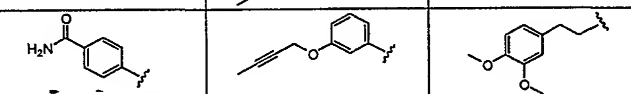
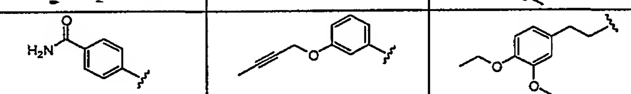
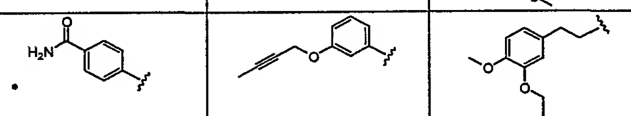
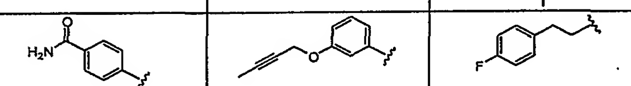
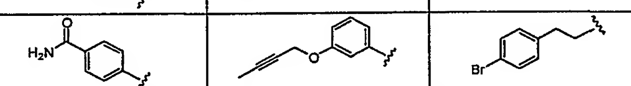
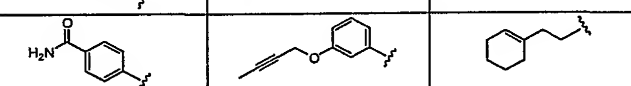
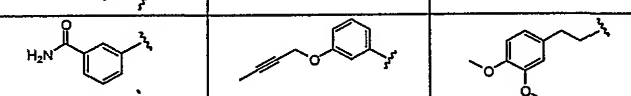
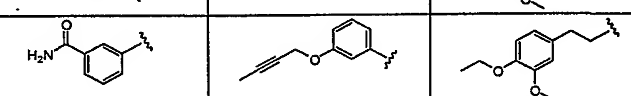
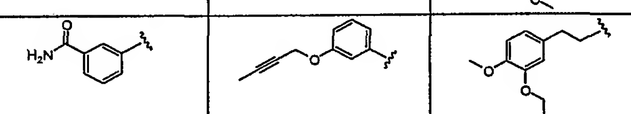
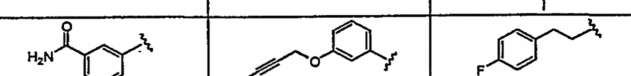
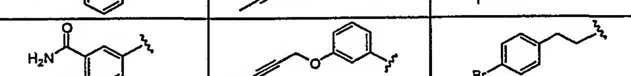
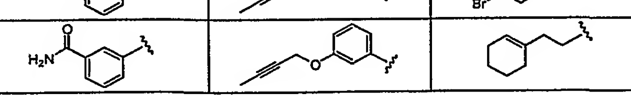
Example 16	R_1	R_2	R_3	LC@254	$(M+H)^+$
C12				3.15 min	590
D12				3.18 min	590
E12				3.26 min	624
F12				3.29 min	624
G12				3.15 min	590
H12				3.18 min	590
I12				3.31 min	624

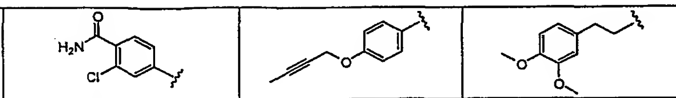
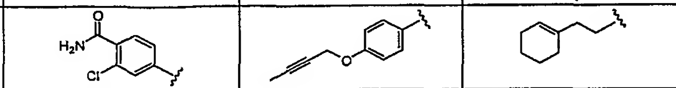
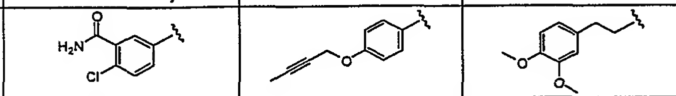
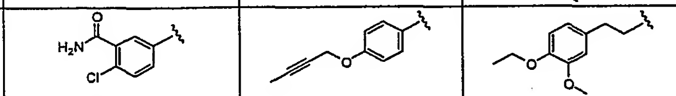
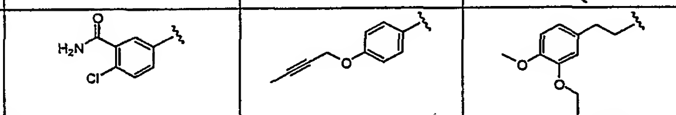
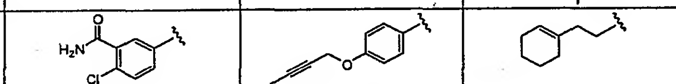
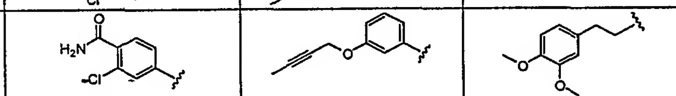
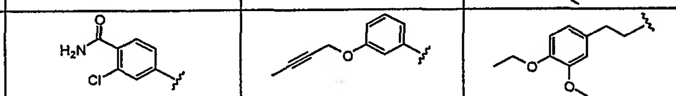
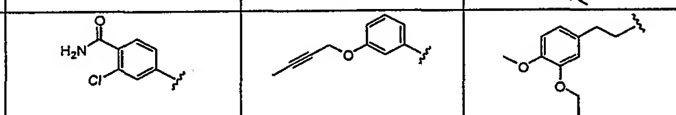
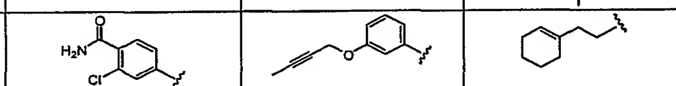
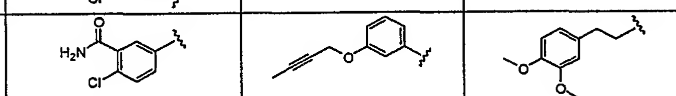
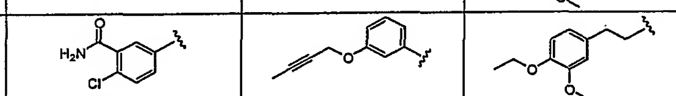
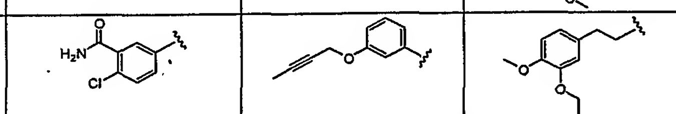
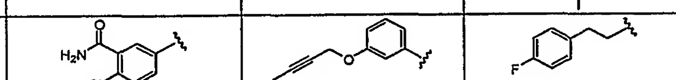
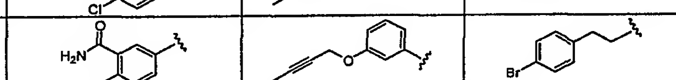
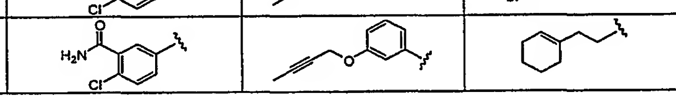
J12				3.29 min	624
K12				3.27 min	534
L12				3.285 min	534
M12				3.39 min	568
N12				3.41 min	568
O12				3.27 min	534
P12				3.29 min	534
Q12				3.40 min	568
R12				3.40 min	568
S12				2.75 min	554
T12				2.76 min	554
U12				2.79 min	554
V12				2.82 min	554
W12				3.14 min	622
X12				3.17 min	622
Y12				3.15 min	622
Z12				3.13 min	622
A13				3.13 min	532
B13				3.15 min	532
C13				3.25 min	566

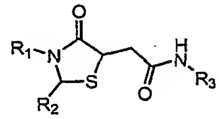
D13				3.26 min	566
E13				3.12 min	532
F13				3.13 min	532
G13				3.24 min	566
H13				3.24 min	566
I13				2.57 min	518
J13				2.59 min 2.70 min	518
K13				2.66 min 2.74 min	552
L13				2.67 min 2.75 min	552
M13				2.59 min	518
N13				2.60 min	518
O13				2.66 min 2.75 min	552
P13				2.68 min	552

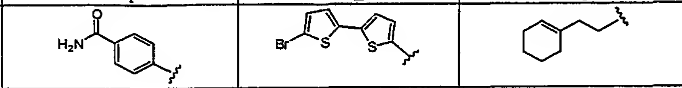
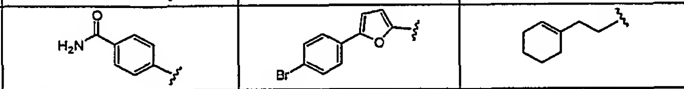
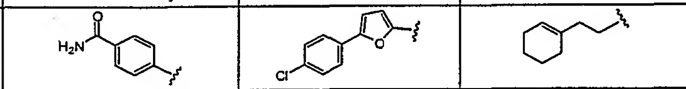
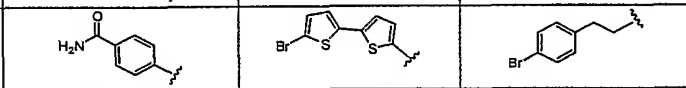
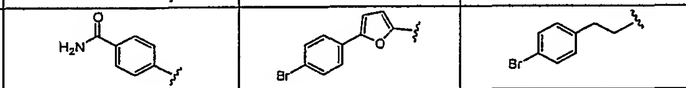
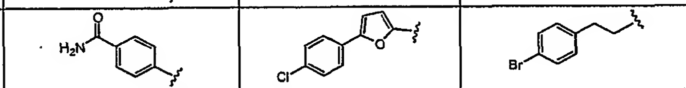
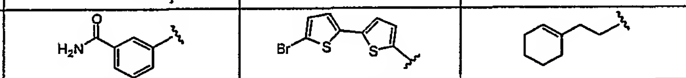
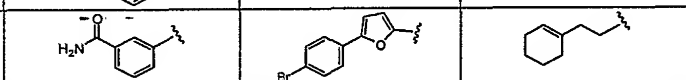
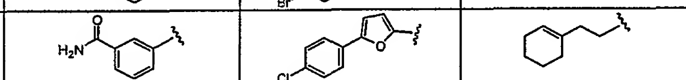
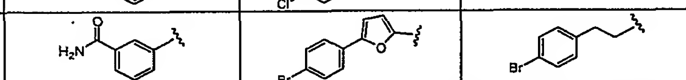
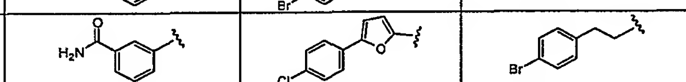
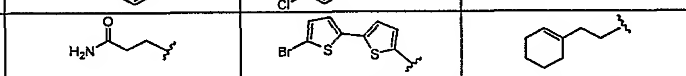
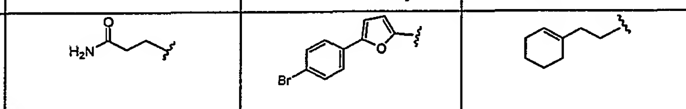
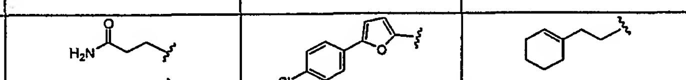
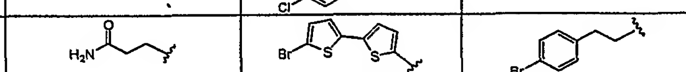
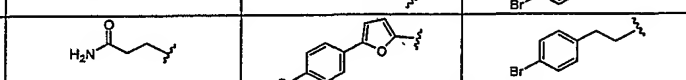
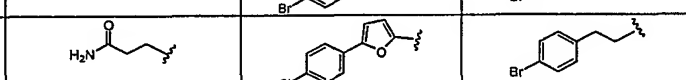
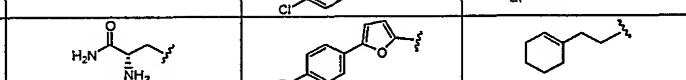
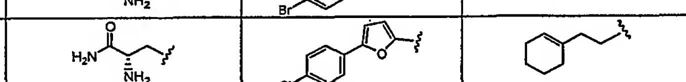
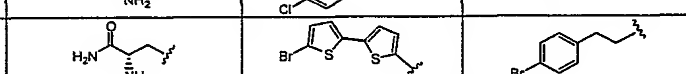
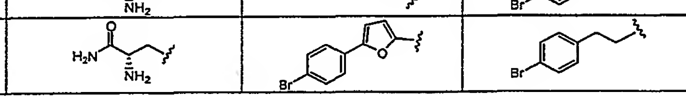


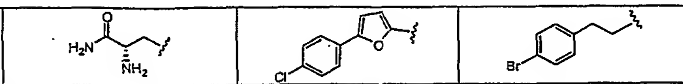
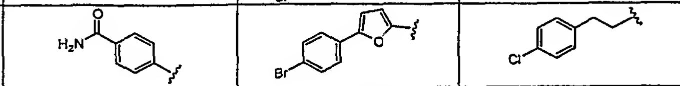
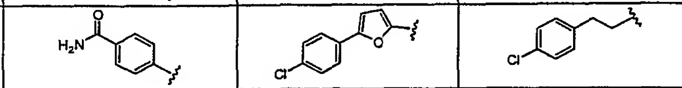
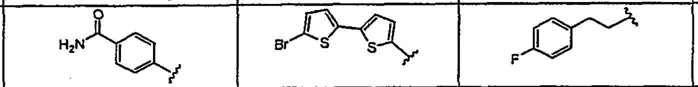
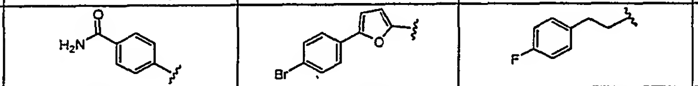
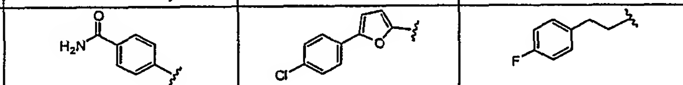
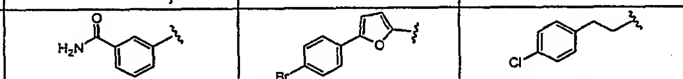
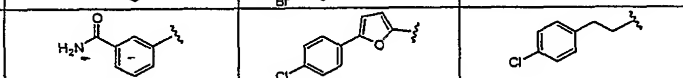
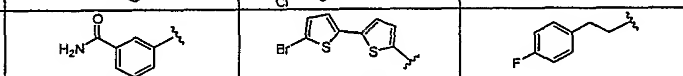
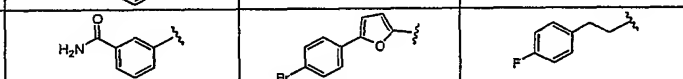
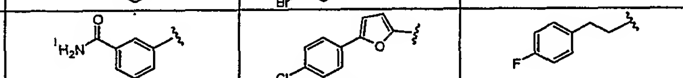
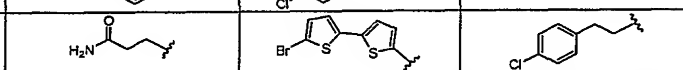
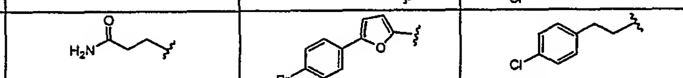
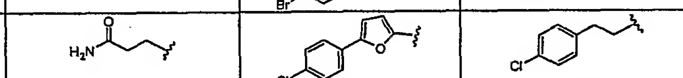
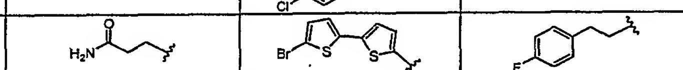
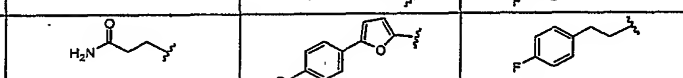
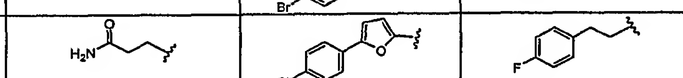
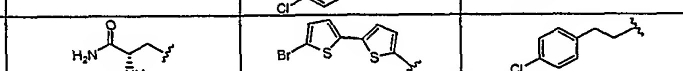
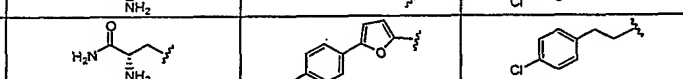
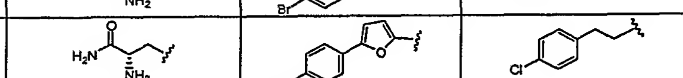
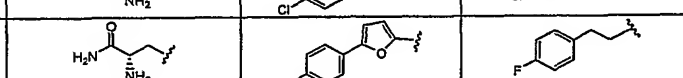
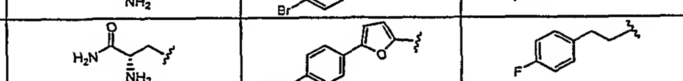
Example16	R_1	R_2	R_3	LC@254	$(M+H)^+$
Q13				2.99 min 3.03 min	588
R13				3.16 min	602
S13				3.16 min	602
T13				3.24 min	546

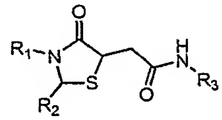
U13				2.77 min	532
V13				3.06 min	588
W13				3.18 min	602
X13				3.17 min	602
Y13				3.44 min	608
Z13				2.71 min 2.79 min	532
A14				3.02 min	588
B14				3.16 min	602
C14				3.14 min	602
D14				3.24 min	546
E14				3.43 min	606
F14				2.73 min	532
G14				3.03 min	588
H14				3.18 min	602
I14				3.16 min	602
J14				3.26 min	546
K14				3.45 min	606
L14				2.69 min 2.75 min	532

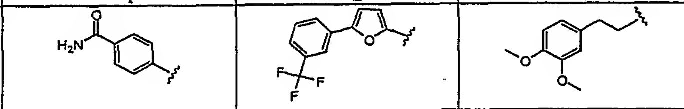
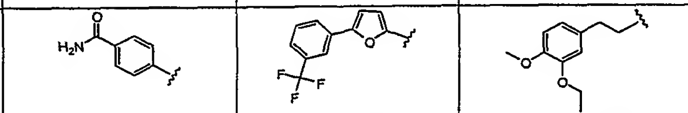
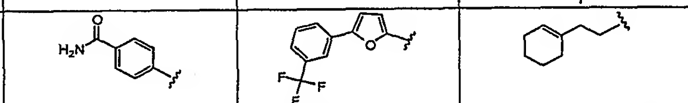
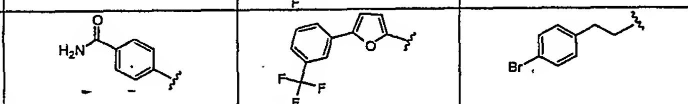
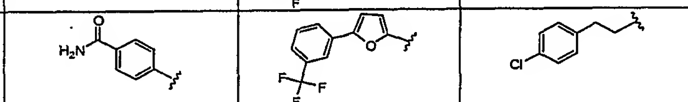
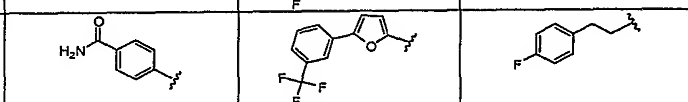
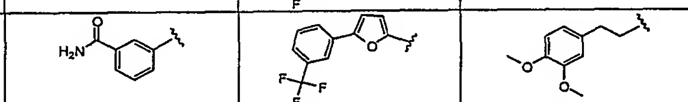
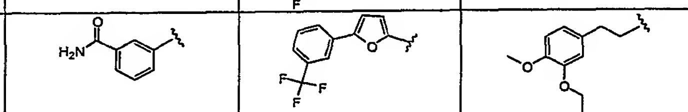
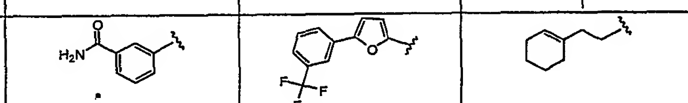
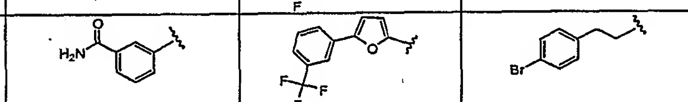
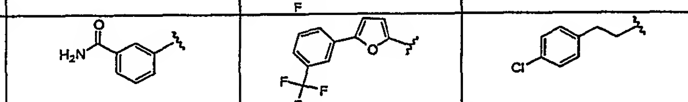
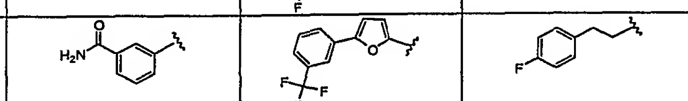
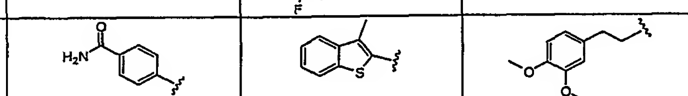
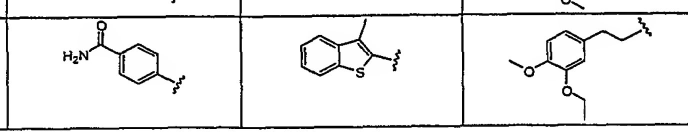
M14				3.15 min	622
N14				2.85 min	566
O14				3.17 min	622
P14				3.31 min	636
Q14				3.30 min	636
R14				2.87 min	566
S14				3.14 min	622
T14				3.29 min	636
U14				3.27 min	636
V14				2.83 min	566
W14				3.17 min	622
X14				3.31 min	636
Y14				3.30 min	636
Z14				3.38 min	580
A15				3.56 min	640
B15				2.86 min	566

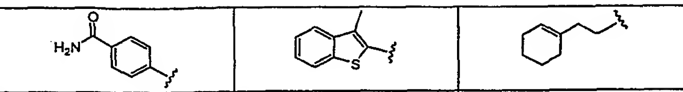
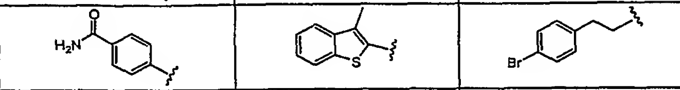
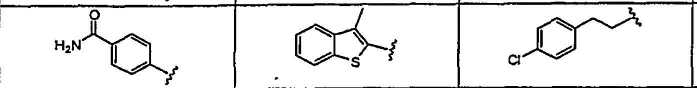
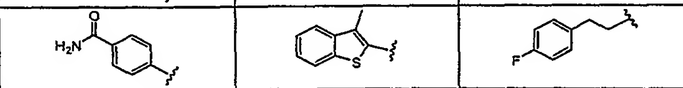
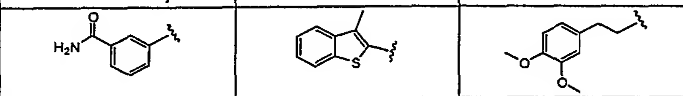
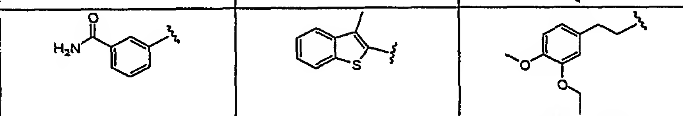
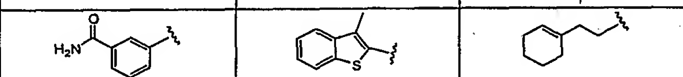
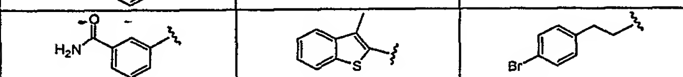
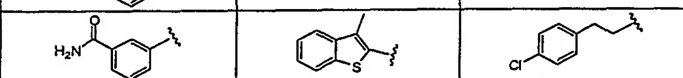
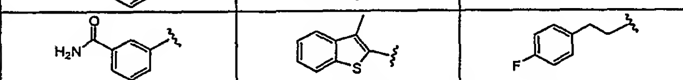
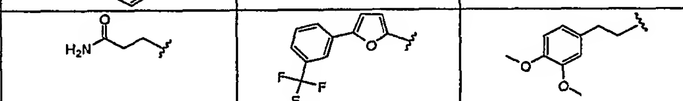
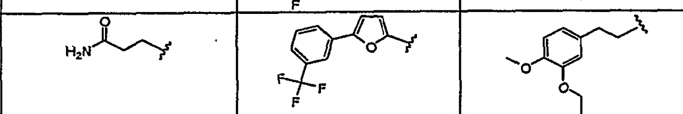
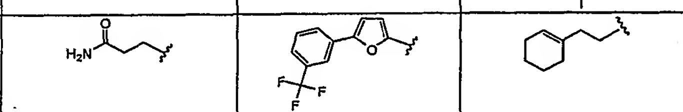
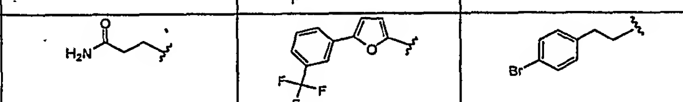
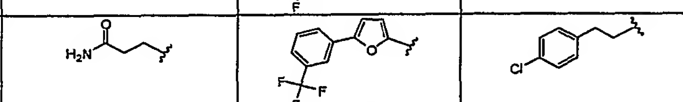
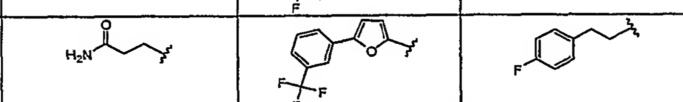
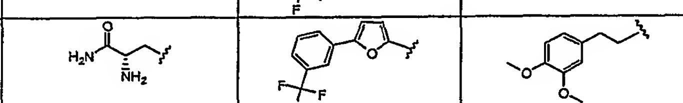
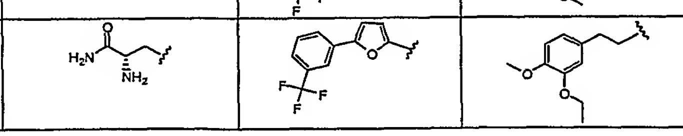


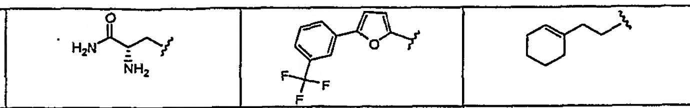
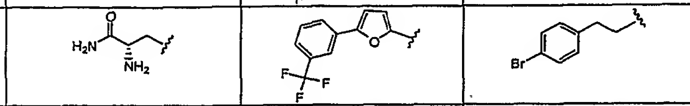
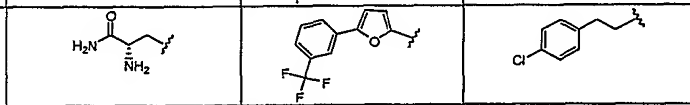
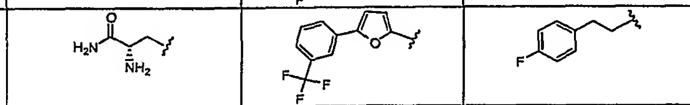
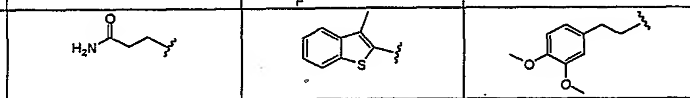
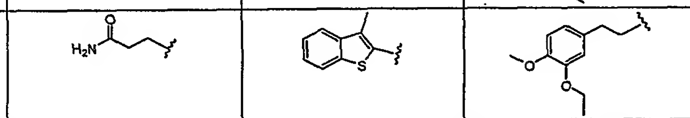
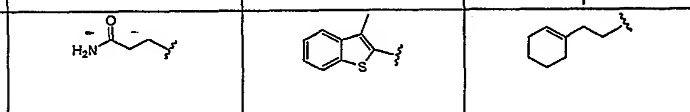
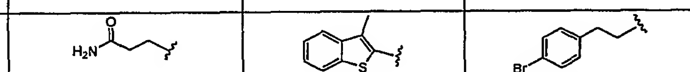
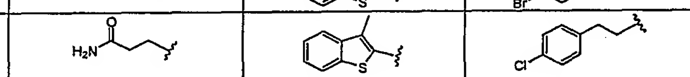
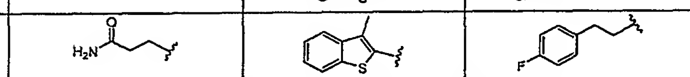
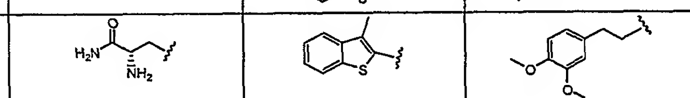
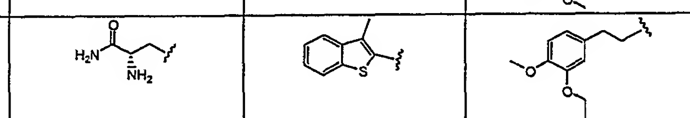
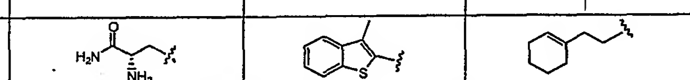
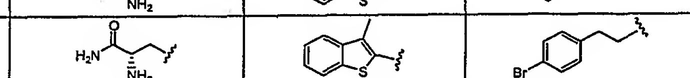
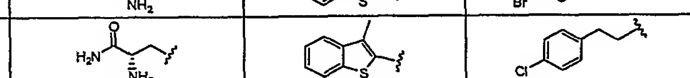
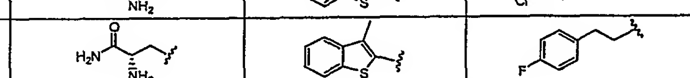
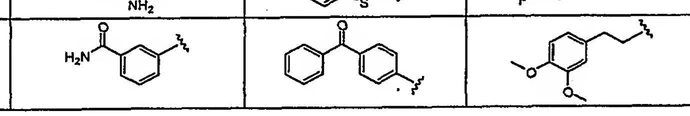
Example 16	R_1	R_2	R_3	LC@254	$(M+H)^+$
C15				3.70 min 3.77 min	630
D15				3.49 min	608
E15				3.49 min 3.53 min	564
F15				4.48 min	706
G15				4.35 min 4.40 min	684
H15				4.36 min	638
I15				3.76 min	630
J15				3.51 min 3.60 min	608
K15				3.54 min 3.58 min	564
L15				4.38 min 4.44 min	684
M15				4.33 min 4.39 min	638
N15				3.70 min 3.80 min	582
O15				3.35 min 3.41 min	560
P15				3.33 min 3.47 min	516
Q15				4.44 min	658
R15				4.24 min	636
S15				4.15 min 4.19 min	590
T15				3.42 min	577
U15				3.40 min 3.53 min	531
V15				3.83 min	673
W15				4.05 min 4.12 min	651

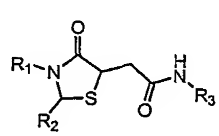
X15				4.09 min 4.13 min	605
Y15				4.29 min 4.36 min	638
Z15				4.25 min 4.31 min	594
A16				4.15 min	644
B16				4.12 min 4.19 min	622
C16				4.07 min 4.13 min	578
D16				4.33 min 4.39 min	638
E16				4.28 min 4.34 min	594
F16				4.20 min	644
G16				4.16 min 4.23 min	622
H16				4.12 min 4.18 min	578
I16				4.39 min	614
J16				4.19 min	590
K16				4.13 min	546
L16				4.22 min	596
M16				3.98 min 4.03 min	574
N16				3.97 min	530
O16				3.79 min	629
P16				4.08 min 4.14 min	607
Q16				4.05 min 4.10 min	563
R16				3.97 min 4.04 min	589.2
S16				3.92 min 4.00 min	545

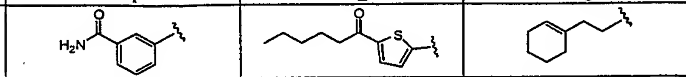
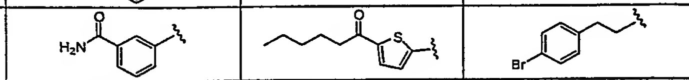
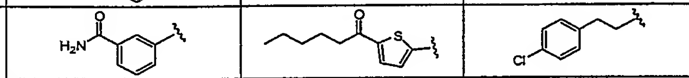
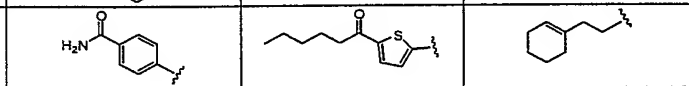
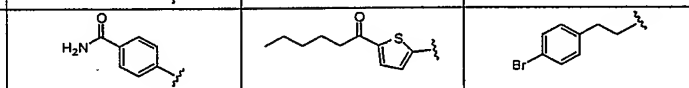
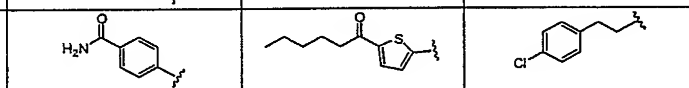
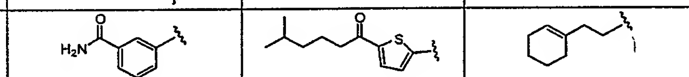
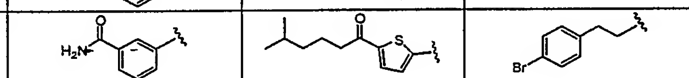
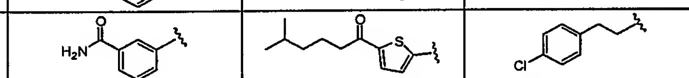
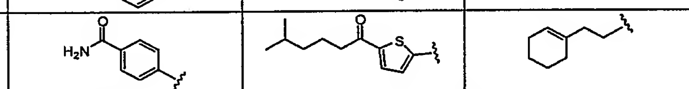
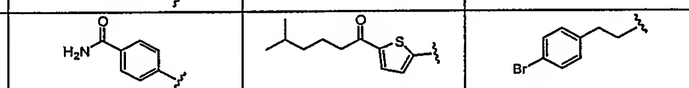
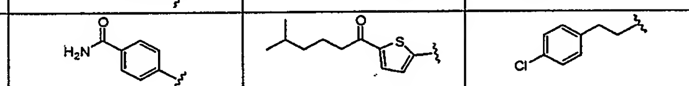
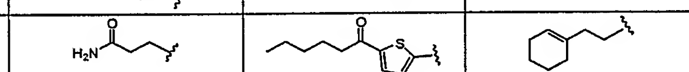
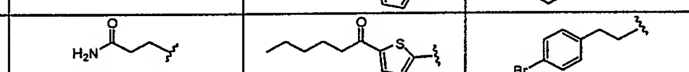
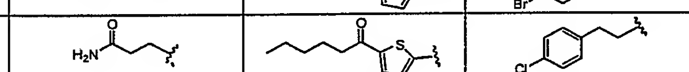
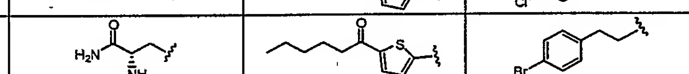
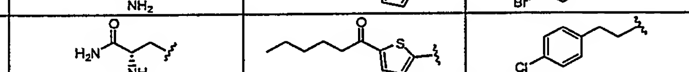
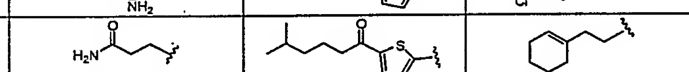
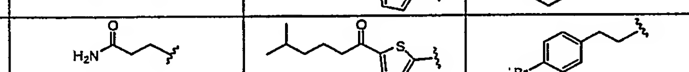
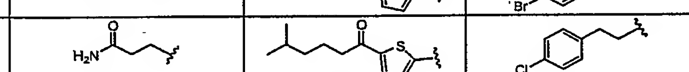
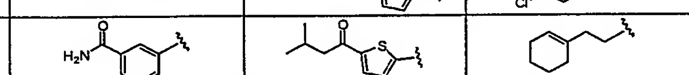
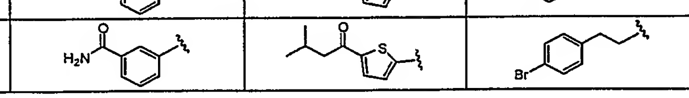


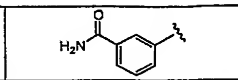
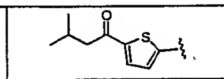
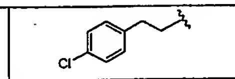
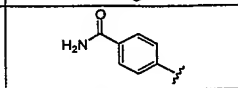
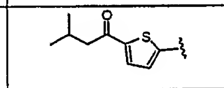
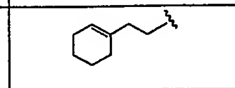
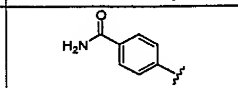
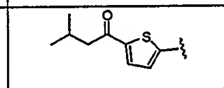
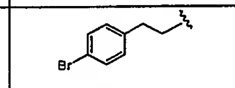
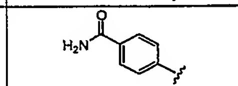
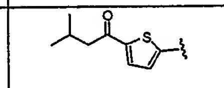
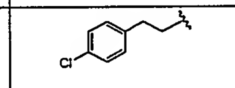
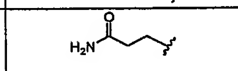
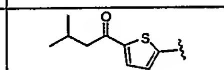
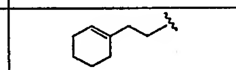
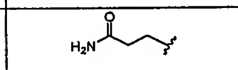
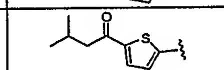
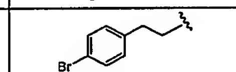
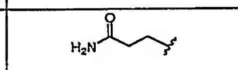
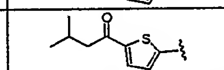
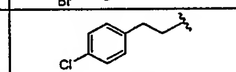
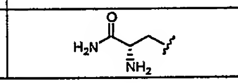
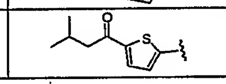
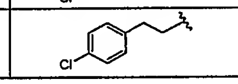
	R$_1$	R$_2$	R$_3$	LC@254	(M+H)$^+$
T16				2.86 min 2.95 min	654
U16				3.01 min 3.09 min	668
V16				2.31 min	598
W16				3.33 min 3.40 min	672
X16				3.29 min 3.35 min	628
Y16				3.18 min	612
Z16				2.90 min 2.99 min	654
A17				3.05 min 3.13 min	668
B17				2.35 min	598
C17				3.37 min 3.44 min	672
D17				3.32 min 3.39 min	628
E17				3.15 min 3.22 min	612
F17				2.57 min 2.66 min	590
G17				2.73 min 2.81 min	604

H17				2.06 min 2.15 min	534
I17				3.08 min 3.14 min	608
J17				3.09 min	564
K17				2.86 min 2.92 min	548
L17				2.61 min 2.71 min	590
M17				2.77 min 2.86 min	604
N17				2.10 min 2.20 min	534
O17				3.12 min 3.18 min	608
P17				3.06 min 3.13 min	564
Q17				2.89 min 2.96 min	548
R17				2.69 min 2.78 min	606
S17				2.85 min 2.93 min	620
T17				2.14 min 2.20 min 2.30 min	550
U17				3.16 min 3.22 min	624
V17				3.11 min 3.17 min	580
W17				2.95 min 3.01 min	564
X17				2.08 min 2.19 min	621
Y17				2.21 min 2.29 min	635

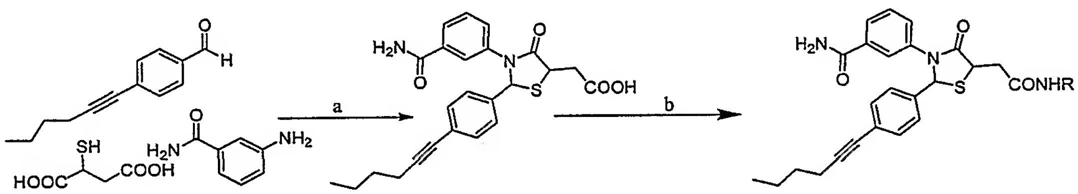
Z17				1.62 min 1.81 min	565
A18				2.46 min 2.51 min	639
B18				2.47 min	596
C18				2.29 min 2.35 min	579
D18				2.41 min 2.48 min	542
E18				2.58 min 2.64 min	556
F18				1.85 min 2.07 min 2.09 min	486
G18				2.97 min	560
H18				2.92 min	516
I18				2.69 min 2.74 min	500
J18				1.76 min 1.83 min	557
K18				1.92 min 1.98 min	571
L18				1.28 min 1.46 min	501
M18				2.26 min	575
N18				2.21 min	531
O18				2.04 min 2.10 min	515
P18				2.73 min 2.78 min	624



	R1	R2	R3	LC@254	$(M+H)^+$
Q18				2.75 min	568
R18				3.35 min	642
S18				3.31 min	598
T18				2.72 min	568
U18				3.32 min	642
V18				3.29 min	598
W18				2.89 min	582
X18				3.48 min	656
Y18				3.44 min	612
Z18				3.25 min	582
A19				4.15 min	656
B19				4.09 min	612
C19				2.93 min	520
D19				3.79 min	594
E19				3.74 min	550
F19				3.21 min	609
G19				3.17 min	565
H19				2.73 min	534
I19				3.36 min	608
J19				3.31 min	564
K19				2.57 min	554
L19				3.17 min	628

M19				3.13 min	584
N19				2.55 min	554
O19				3.14 min	628
P19				3.10 min	584
Q19				2.41 min	506
R19				3.02 min	580
S19				2.98 min	536
T19				2.61 min	551

Scheme 1. For Examples 17-19



a) CH_3CN, 80^0C; b) RNH_2, HATU, DIAE, DMF

Example 17

Preparation of [3-[3-{aminocarbonyl}phenyl-2-{4-hex-1-ynyl}phenyl]-4-oxo-1, 3-thiazolidin-5-yl] acetic acid.

A solution of 3-aminobenzamide (5.4 g , 40 mmol) ,4-hex-1-yn-1-yl-benzaldehyde (7.3 g, 40 mmol), and mercaptosuccinic acid (18 g, 120 mmol) in acetonitrile (250 mL) was heated to reflux for 48 hours. After cooling to room temperature, the mixture was concentrated in vacuo and the residue was crystallized from methanol to afford the title compound, m.p 210-212 ^0C.^1H NMR (DMSO-d_6) δ 0.94 (t, J = 7.1 Hz, 3H),1.50 (m, 4 H), 2.44 (t , J = 6.7 Hz, 2 H), 2.96 (dd, J=17.3, 8.5 Hz, 1H), 3.13 (dd, J = 17.3, 3.8 Hz, 1H), 4.58 (dd, J = 8.2, 3.4 Hz,1 H), 6.53 (s,1 H), 7.33 (d, J=8.1 Hz, 1H), 7.45 (m , 5H), 7.73 (d, J = 7.2 Hz, 1H), 7.90 (s, 1H), 8.01 (s , 1H), 12.77 (broad s, 1H). MS (FI NEG) m/z 435 $(M-Z)^-$.

Example 18

Preparation of 3-[(2S*, 5 R*)-5(2-{3-ethoxy-4-methoxyphenyl}-ethylamino-2-oxoethyl)-2-{4-hex-1-ynylphenyl}-4-oxo-1,-3-thiazolidin-3-yl]benzamide.

A solution of [3-[3-{aminocarbonyl}phenyl-2-{4-hex-1-ynyl}phenyl]-4-oxo-1, 3-thiazolidin-5-yl] acetic acid (1.8 g, 4.1 mmol), and 1,8-diazabicyclo[5.4.0]-undec-7-ene (0.57 g, 3.7 mmol) in methanol (225 mL) and dimethylformamide (25 mL) was stirred at room temperature for 60 hours. The solution was concentrated in vacuo , the residue was triturated with methylene chloride and 1 N hydrochloric acid, and the solid crude product, a mixture of trans and cis isomers in a ratio 2.3/1, was collected by filtration and dried. A solution of this crude product, 3-ethoxy-4-methoxyphenethyl-amine (0.9 g, 4.6 mmol), diisopropylethylamine (0.58 g, 4.6 mmol), and O-(7-azabenzotriazol-1-yl)-N,N,N',N-tetramethyluronium hexafluorophosphate (2.7 g, 5.8 mmol) in dimethylformamide (30 mL) was stirred at room temperature for 20 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography (Zorpax PRO C18, acetonitrile/water 60/40) to afford the title compound (0.46 g, 18%) m.p.130-133^{0}C.^{1}H NMR (DMSO-d_6) δ 0.87 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3 H), 1.42 (m, 4 H), 2.39 (t, J = 6.8 Hz, 2 H), 2.63 (t, J = 7.1 Hz , 2 H), 2.71 (dd, J = 15.5, 9.7 Hz, 1H), 3.06 (dd, J = 14.5, 3.6 Hz, 1H), 3.26 (q, J = 6.4 Hz, 2H), 3.70 (s, 3H), 3.94 (q, J = 7.0 Hz, 2H), 4.39 (dd, J = 9.3, 3.5 Hz1H), 6.49 (s, 1H), 6.73 (m, 3H), 7.24 (d, J = 8.2 Hz, 2H), 7.40 (m, 5H), 7.64 (d, J = 7.5 Hz, 1H), 7.81 (s, 1H), 7.93 (s, 1H), 8.15 (t, J = 5.5 Hz, 1H), 7.81 (s, 1H), 7.93 (s, 1H), 8.15 (t, J = 5.5 Hz,1H); .MS (FI POS) m/z 614(M+H); Anal.Calc. for $C_{24}H_{24}N_2O_4S$. C: 66.04, H: 5.54, N: 6.42, found. C: 65.83, H: 5.67, N: 6.09.

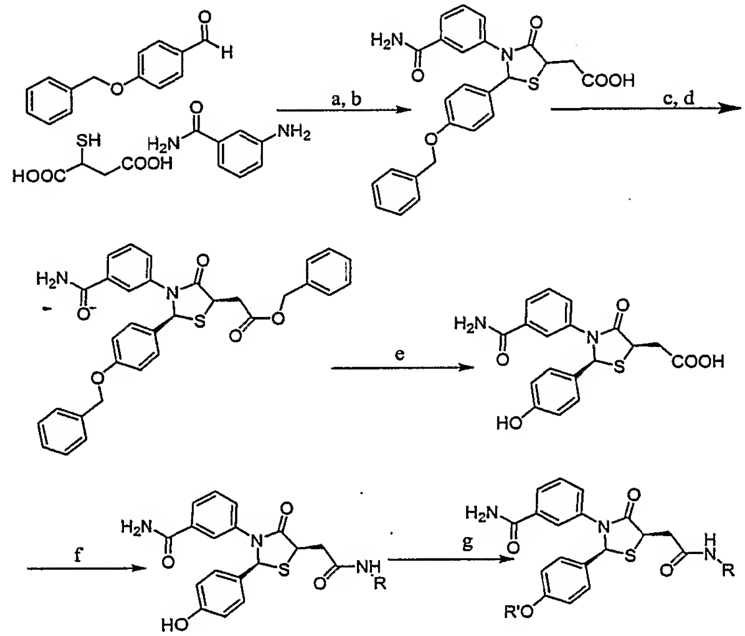
Example 19

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(4-ethoxy-3-methoxyphenyl)ethyl]-amino}-2-oxoethyl)-2)-4-hex-1-ynylphenyl)-4-oxo-1,3-thiazolidn-3-yl]benzamide.

Similar to the above example[3-[3-{aminocarbonyl}phenyl-2-{4-hex-1-ynyl}phenyl]-4-oxo-1, 3-thiazolidin-5-yl] acetic acid (3.7 g,8.2 mmol), 4-ethoxy-3-methoxyphenethylamine (2.12 g, 16.4 mmol), and O-(7-azabenzotriazol-1-yl)-N,N,N^1,N^1-tetramethyluronium-hexafluorophosphate (4.11 g, 10.8 mmol) were reacted to obtain the title compound (1.4 g, 28%); m.p. 154-157 ^{0}C. ^{1}H NMR (DMSO-d_6) δ 0.87 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.0 Hz, 3H), 1.43 (m, 4H), 2.37 (t, J = 6.8 Hz, 2H), 2.64 (t, J = 7.2 Hz,

2H), 3.07 (dd, J = 15.6, 3.5 Hz, s, 1H), 3.27 (q, J = 6.6 Hz, 2H), 3.69 (s, 3H), 3.93 (q, J = 7.0 Hz, 2H), 4.39 (dd, J = 9.7, 3.5 Hz, 1H), 6.49 (s, 1H), 6.73 (m, 3H), 7.24 (d, J = 8.2 Hz, 2H), 7.38 (m, 5H), 7.64 (d, J = 7.5 Hz, 1H), 7.82 (s, 1H), 7.93 (s, 1H), 8.16 (t, J = 5.5 Hz, 1H).; MS (FIPOS) m/z 614 (M+H): Anal.Calc. for $C_{35}H_{39}N_3O_5S$ C: 68.49, H: 6.40, N: 6.85, found. C: 68.15, H: 6.42, N: 6.78.

Scheme 2. For Examples 20-37, 43-47.



a) CH_3CN, mole. sieves 4A, 80^{0}C; **b)** DBU, MeOH, THF, 70^{0}C; **c)** $PhCH_2Br$, K_2CO_3; **d)** recrystalize from EtOAc; **e)** TFA, thioanisole; **f)** RNH_2, HATU, DIAE, DMF; **g)** R'X, K_2CO_3, DMF

Example 20

Preparation of {(2S*,5S*)-3-[3-(aminocarbonyl) phenyl]-2-[4-(benzyloxy) phenyl]-4-oxo-1,3-thiazolidin-5-yl} acetic acid.

A round-bottomed flask was fitted with a bump trap containing molecular sieves (4A). 3-aminobenzamide (5.4 g, 40 mmol) and 4-benzyloxybenzaldehyde (10.2 g, 48 mmol) were added to the flask and allowed to stir in acetonitrile (300 mL) at 80°C for 1 hour. Mercaptosuccinic acid (18.0 g, 120 mmol) was added to the reaction mixture. The solution was allowed to stir for 48 hours. The suspension was cooled in an ice-water bath for 1 hour and filtered, yielding the title compound (11.8g, 64%) as a white solid. ^{1}H NMR (DMSO-d_6):δ 12.49 (bs, 1H), 7.93 (b, 1H), 7.80 (s, 1H), 7.64 (d, 1H, 8Hz), 7.30-7.42 (m, 10H), 6.87 (d, 1H, 8Hz), 6.45 (s, 1H), 4.95 (s, 2H), 4.50 (dd, 1H, 9Hz, 3Hz), 3.15 (dd, 1H,

18Hz, 4Hz), 2.80 (dd, 1H, 18Hz, 9Hz). MS (FI-NEG):$[M-H]^-$= 461.Anal.Calc. for $C_{25}H_{22}N_2O_5S$: C, 64.92, H, 4.79, N, 6.06. Found: C, 61.52, H, 4.35, N, 8.89.

Example 21

Preparation of {(2S*,5R*)-3-[3-(aminocarbonyl) phenyl]-2-[4-(benzyloxy) phenyl]-4-oxo-1,3-thiazolidin-5-yl} acetic acid.

{(2,5-Trans)-3-[3-(aminocarbonyl) phenyl]-2-[4-(benzyloxy) phenyl]-4-oxo-1,3-thiazolidin-5-yl} acetic acid (3.0 g, 6.5 mmol) was dissolved in methanol (100 mL) and THF (100 mL) at 70°C. DBU (11.9 g, 78 mmol) was added, and the solution was allowed to stir for 48 hours. Analytical HPLC (isocratic, 40% acetonitrile/water) showed two components in a 60:40 ratio. The more abundant material proved upon co-injection to be the *trans* epimer. The solvent was removed under vacuum, and the oil remaining was partitioned between ethyl acetate and 3 N HCl. The ethyl acetate fraction was washed two additional times with acid. The organic layer was separated, washed with brine and dried using $MgSO_4$. The solvent was removed under reduced pressure, yielding a mixture of *cis* and *trans* epimers as a white solid. Preparative HPLC (isocratic, 40% acetonitrile/water) was performed on this material, purifying the title compound (830 mg, 28%). ^{1}H NMR (DMSO-d_6): δ 7.93 (b, 1H), 7.80 (s, 1H), 7.64(d, 1H, 8Hz), 7.30-7.42 (m, 10H), 6.87 (d, 1H, 8Hz), 6.45 (s, 1H), 5.00 (s, 2H), 4.40 (dd,1H, 9Hz, 3Hz), 3.15 (dd, 1H, 18Hz, 4Hz), 2.80 (dd, 1H, 18Hz, 9Hz). MS (FI-NEG):$[M-H]^-$= 461.Anal. Calc. for $C_{25}H_{22}N_2O_5S$: C, 64.92, H, 4.79, N, 6.06. Found: C, 61.30, H, 4.64, N, 5.71.

Example 22

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl]-amino}-2-oxoethyl)-2-(4-benzyloxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

{(2S*,5R*)-3-[3-(aminocarbonyl) phenyl]-2-[benzyloxyphenyl]-4-oxo-1,3-thiazolidin-5-yl} acetic acid (8.00 g, 17.3 mmol) was dissolved in methanol (150 mL) and THF (150 mL) at 80°C. DBU (31.6 g, 208 mmol) was added, and the solution was allowed to stir for 15h. Analytical HPLC (isocratic, 45% acetonitrile/water) showed two components in a 60:40 ratio. The solvent was removed under vacuum, and the oil remaining was partitioned between ethyl acetate and 3 N HCl. The ethyl acetate fraction was washed two additional times with acid. The organic layer was separated, washed with brine and dried using $MgSO_4$. The solvent was removed under reduced pressure, yielding a mixture of *cis* and *trans* epimers as a white solid. This crude material was dissolved in

DMF (100 mL) with DIEA (3.06 g, 23 mmol) and 3-ethoxy-4-methoxyphenethylamine (4.29 g, 23 mmol). HATU (8.7 g, 23 mmol) was added and the solution was allowed to stir at room temperature for 15 h. The DMF solution was partitioned between ethyl acetate and brine twice, and the organic layer was washed twice with 3N HCl. The organic layer was washed again with brine and dried using $MgSO_4$. The solvent was removed under vacuum, yielding the crude products as a yellow oil. A portion of this mixture (4 g) was purified using preparative HPLC (40 acetonitrile/water (.1% TFA)) to yield the title product (1.10 g, 37%). The *cis* epimer:^{1}H NMR (DMSO-d_6): δ 8.15 (m, 1H), 7.92 (bs, 1H), 7.72 (s, 1H), 7.62 (d, 1H, 8Hz), 7.30-7.42 (m, 9H), 6.70-6.82 (m, 4H), 6.43 (s, 1H), 4.37 (dd, 1H, 9Hz, 3Hz), 3.99 (q, 2H, 8 Hz), 3.64 (s, 3H), 3.26 (m, 2H), 3.15 (dd, 1H, 18Hz, 4Hz), 2.80 (dd, 1H, 18Hz, 9Hz), 2.62 (m, 2H), 1.32 (t, 3H, 8 Hz). MS (ESI-NEG):$[M-H]^-$= 639. Anal.Calc. for $C_{36}H_{37}N_3O_6S$: C, 67.59, H, 5.83, N, 6.57. Found: C, 67.16, H, 5.82, N, 6.39.

Example 23

Preparation of 3-[(2S*,5S*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl]-amino}-2-oxoethyl)-2-(4-benzyloxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

{(2S*, 5S*)-3-[3-(aminocarbonyl) phenyl]-2-[benzyloxyphenyl]-4-oxo-1,3-thiazolidin-5-yl} acetic acid (8.00 g, 17.3 mmol) was dissolved in methanol (150 mL) and THF (150 mL) at 80°C. DBU (31.6 g, 208 mmol) was added, and the solution was allowed to stir for 15 hours. Analytical HPLC (isocratic, 45% acetonitrile/water) showed two components in a 60:40 ratio. The solvent was removed under vacuum, and the oil remaining was partitioned between ethyl acetate and 3 N HCl. The ethyl acetate fraction was washed two additional times with acid. The organic layer was separated, washed with brine and dried using $MgSO_4$. The solvent was removed under reduced pressure, yielding a mixture of cis and trans epimers as a white solid. This crude material was dissolved in DMF (100 mL) with DIEA (3.06 g, 23 mmol) and 3-ethoxy-4-methoxyphenethylamine (4.29 g, 23 mmol). HATU (8.7g, 23 mmol) was added and the solution was allowed to stir at room temperature for 15 h. The DMF solution was partitioned between ethyl acetate and brine twice, and the organic layer was washed twice with 3N HCl. The organic layer was washed again with brine and dried using $MgSO_4$. The solvent was removed under vacuum, yielding the crude products as a yellow oil. A portion of this mixture (4 g) was purified using preparative HPLC (40 acetonitrile/water (.1% TFA)) to yield the trans title product (1.52 g, 51%). ^{1}H NMR (DMSO-d_6): δ 8.15 (m, 1H), 7.92 (bs, 1H), 7.72 (s, 1H), 7.62 (d,

1H, 8Hz), 7.30-7.42 (m, 9H), 6.70-6.82 (m, 4H), 6.39 (s, 1H), 4.46 (m, 1H), 3.99 (q, 2H, 8 Hz), 3.64 (s, 3H), 3.26 (m, 2H), 3.15 (dd, 1H,18Hz, 4Hz), 2.80 (dd, 1H, 18Hz, 9Hz), 2.62 (m, 2H), 1.32 (t, 3H, 8 Hz). MS (ESI-NEG):$[M-H]^-$= 639. Anal.Calc. for $C_{36}H_{37}N_3O_6S$: C, 67.59, H, 5.83, N, 6.57. Found: C, 65.68, H, 5.63, N, 6.22.

Example 24

Preparation of benzyl {(2S*,5R*)-3-[3-(aminocarbonyl) phenyl]-2-[4-(benzyloxy) phenyl]-4-oxo-1,3-thiazolidin-5-yl} acetate.

{(2S*,5S*)-3-[3-(aminocarbonyl) phenyl]-2-[benzyloxyphenyl]-4-oxo-1,3-thiazolidin-5-yl} acetic acid (500 mg, 1.1 mmol) was dissolved in methanol (10 mL) and THF (10 mL) at 80°C. DBU (1.87 g, 12.3 mmol) was added, and the solution was allowed to stir for 15 hours. Analytical HPLC (isocratic, 45% acetonitrile/water) showed two components in a 60:40 ratio. The solvent was removed under vacuum, and the oil remaining was partitioned between ethyl acetate and 3 N HCl. The ethyl acetate fraction was washed two additional times with acid. The organic layer was separated, washed with brine and dried using $MgSO_4$. The solvent was removed under reduced pressure, yielding a mixture of cis and trans epimers as a white solid. This material was dissolved in DMF (10 ml) and K_2CO_3 (280 mg, 2 mmol) and benzyl bromide (340 mg, 2 mmol) were added. After 3h, the reaction was complete. The DMF was partitioned between ethyl acetate and brine twice. The organic layer was washed with 3N HCl twice. The organic layer was washed with brine, dried over MgSO4 and concentrated under vacuum to yield an oil. The oil was triturated in ether (180 mL) for 1 hour. This suspension was filtered, yielding a white powdery solid. This material was dissolved in ethyl acetate (20 ml) with heating. It was placed in a freezer for 2 hours and then filtered. The ratio of *cis:trans* was increased significantly. This recrystallization was repeated twice, yielding the title compound (60 mg, 10%) as the pure *cis* epimer. ^{1}H NMR (DMSO-d_6):δ 7.93 (1H, b), 7.80 (1H, s), 7.62 (d, 1H, 8Hz), 7.30-7.42 (m, 15H), 6.87 (d, 1H, 8 Hz), 6.45 (s, 1H), 5.17 (d, 2H, 3 Hz), 4.99 (s, 2H), 4.45 (dd, 1H, 9Hz, 3Hz), 3.15 (dd, 1H, 18 Hz, 4Hz), 2.80 (dd, 1H, 18Hz, 9Hz). MS (ESI-POS):$[M+H]^+$= 553. Anal. Calc. for $C_{32}H_{28}N_2O_5S$: C, 69.55, H, 5.11, N, 5.07. Found: C, 68.54, H, 4.81, N, 4.95.

Example 25

Preparation of [(2S*,5R*)-3-[3-(aminocarbonyl) phenyl]-2-(4-(hydroxyphenyl)-4-oxo-1,3-thiazolidin-5-yl] acetic acid.

Benzyl {(2S*,5R*)-3-[3-(aminocarbonyl) phenyl]-2-[4-(benzyloxy) phenyl]-4-oxo-1, 3-thiazolidin-5-yl} acetate (1.0 g , 1.8 mmol) was dissolved in trifluoroacetic acid (15 mL) and thioanisole (1.8 g, 15 mmol) at room temperature. This solution was allowed to stir for 24 hours. The solvent was removed under vacuum, leaving a pale yellow oil. This oil was dripped into stirring diethyl ether, and this suspension was allowed to stir for 24 hours. This mixture was filtered, yielding the title compound (640 mg, 95%) as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 12.32 (bs, 1H), 9.64 (bs, 1H), 7.93 (bs, 1H), 7.78 (s, 1H), 7.62 (d, 1H, 8Hz), 7.30-7.42 (m, 4H), 7.23 (d, 2H, 9Hz), 6.62 (d, 1H, 8Hz), 6.38 (s, 1H), 4.45 (dd, 1H, 9Hz, 3Hz), 3.15 (dd, 1H,18Hz, 4Hz), 2.80 (dd, 1H,18Hz, 9Hz). MS (ESI-POS):[M-H]$^-$= 371. Anal.Calc. for $C_{18}H_{16}N_2O_5S$: C, 58.06, H, 4.33, N, 7.52. Found: C, 57.90, H, 4.34, N, 5.20.

Example 26

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl]amino}-2-oxoethyl)-2-(4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide..

[(2S*,5R*)-3-[3-(aminocarbonyl) phenyl]-2-(4-(hydroxyphenyl)-4-oxo-1,3-thiazolidin-5-yl] acetic acid (650 mg, 1.8 mmol) was dissolved in DMF (15 mL) with DIEA (270 mg, 2.1 mmol) and 3-ethoxy-4-methoxyphenethylamine (270 mg, 2.1 mmol). HATU (811 mg, 2.1 mmol) was added and the solution was allowed to stir at room temperature for 15 hours. The DMF solution was partitioned between ethyl acetate and brine twice, and the organic layer was washed twice with 3N HCl. The organic layer was washed again with brine and dried using $MgSO_4$. The solvent was removed under vacuum, yielding the crude product as a yellow oil. The title product (317 mg, 32%) was purified using silica gel flash chromatography (3% methanol: DCM). ^{1}H NMR (DMSO-d_6): δ 8.15 (m, 1H), 7.92 (bs, 1H), 7.72 (s, 1H), 7.62 (d, 1H, 8Hz), 7.30-7.42 (m, 3H), 7.23 (d, 2H, 9Hz), 6.70-6.82 (m, 3H), 6.69 (d, 1H, 8Hz), 6.35 (s, 1H), 4.44 (dd, 1H, 9Hz, 3Hz), 3.99 (q, 2H, 8 Hz), 3.64 (s, 3H), 3.26 (m, 2H), 3.15 (dd, 1H, 18Hz, 4Hz), 2.80 (dd, 1H, 18Hz, 9Hz), 2.62 (m, 2H), 1.32 (t, 3H, 8 Hz). MS (ESI-NEG):[M-H]$^-$= 550. Anal. Calc. for $C_{29}H_{31}N_3O_6S$: C, 63.37, H, 5.68, N, 7.64. Found: C, 61.57, H, 6.19, N, 6.87.

Example 27

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl]amino}-2-oxoethyl)-2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl) ethyl]amino}-2-oxoethyl)-2-(4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide (50 mg, .09 mmol) was dissolved in DMF (1 mL) with methyl iodide (28 mg, .2 mmol). Potassium carbonate (28 mg, .2 mmol, dissolved in .5 mL of water) was added. The reaction mixture was allowed to stir under nitrogen for 24 hours. The DMF solution was partitioned between ethyl acetate and brine twice, and the organic layer dried using magnesium sulfate. The solvent was removed under vacuum. The crude material was purified using silica gel flash chromotography (3% methanol:DCM), yielding the title compound (32 mg, 60%) as a yellow oil. ^{1}H NMR (DMSO-d_6): δ 8.15 (m, 1H), 7.92 (bs, 1H), 7.72 (s, 1H), 7.62 (d, 1H, 8Hz), 7.30-7.42 (m, 3H), 7.23 (d, 2H, 9Hz), 6.70-6.82 (m, 3H), 6.69 (d, 1H, 8Hz), 6.35 (s, 1H), 4.44 (dd, 1H, 9Hz, 3Hz), 3.99 (q, 2H, 8 Hz), 3.64 (s, 3H), 3.60 (s, 3H), 3.15 (dd, 1H, 18Hz, 4Hz), 2.80 (dd, 1H, 18Hz, 9Hz), 2.62 (m, 2H), 1.32 (t, 3H, 8 Hz). MS (ESI-POS):$[M+H]^+$= 564.

The above procedure was used, varying the alkylating agents, to make the following examples:

<u>Example 28</u>

Preparation of 3-[(2,5-cis)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl) ethyl] amino}-2-oxoethyl)-2-(4-ethoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

From ethyl iodide (71%): MS (ESI-POS): $[M+H]^+$= 578

<u>Example 29</u>

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl) ethyl] amino}-2-oxoethyl)-2-(4-allyloxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl] benzamide.

From allyl bromide (47%): MS (ESI-POS): $[M+H]^+$= 590

<u>Example 30</u>

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl) ethyl] amino}-2-oxoethyl)-2-(4-isopropoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

From isopropyl iodide (38%): MS (ESI-POS): $[M+H]^+$= 592

<u>Example 31</u>

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl) ethyl] amino}-2-oxoethyl)-2-(4-(2,2,2-trifluoroethoxy) phenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

From 2,2,2-trifluoroethyl triflate (22%): MS (ESI-POS): $[M+H]^+= 632$

Example 32

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl) ethyl]amino}-2-oxoethyl)-2-(4-prop-2-ynloxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benza mide.

From propynyl bromide (48%): MS (ESI-POS): $[M+H]^+= 588$

Example 33

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl) ethyl] amino}-2-oxoethyl)-2-(4-but-2-ynloxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

From but-2-ynl bromide (18%): MS (ESI-POS): $[M+H]^+= 602$

Example 34

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl) ethyl] amino}-2-oxoethyl)-2-(4-[(2-methylprop-2-enyl)oxy]phenyl}-4-oxo-1,3-thiazolidin-3-yl] benzamide.

From 2-methyl-prop-2-enyl bromide (23%): MS (ESI-POS): $[M+H]^+= 604$

Example 35

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl) ethyl]amino}-2-oxoethyl)-2-(4-(cyclopropylmethoxy) phenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

From cyclopropyl methyl bromide (38%): MS (ESI-POS): $[M+H]^+= 604$

Example 36

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl) ethyl] amino}-2-oxoethyl)-2-(4-butoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

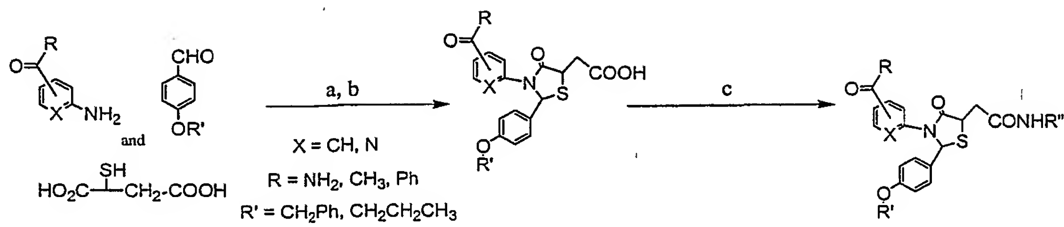
From 2-iodobutane (30%): MS (ESI-POS): $[M+H]^+= 606$

Example 37

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl) ethyl] amino}-2-oxoethyl)-2-(4-isobutoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

From isobutyl iodide (21%): MS (ESI-POS): $[M+H]^+= 606$

Scheme 3. For Examples 38-42, 76-79



a) CH_3CN, mole. sieves 4A, 80^{0}C; **b)** DBU, MeOH, THF, 70^{0}C; **c)** RNH_2, HATU, DIAE, DMF.

Example 38

Preparation of {(2S*,5S*)-3-[3-(aminocarbonyl) phenyl]-2-[4-propoxyphenyl]-4-oxo-1, 3-thiazolidin-5-yl} acetic acid.

A round-bottomed flask was fitted with a bump trap containing molecular sieves (4A). 3-aminobenzamide (1.09 g, 8 mmol) and 4-propoxy-benzaldehyde (1.57 g, 9.6 mmol) were allowed to stir in acetonitrile (60 mL) at 80°C for 1 hour. Mercaptosuccinic acid (3.6 g, 24 mmol) was added to the reaction mixture. The solution was allowed to stir for 24 hours. The suspension was cooled in an ice-water bath for 1 hour and filtered, yielding the title compound (1.90 g, 59%) as a white solid. ^{1}H NMR (DMSO-d_6): δ 12.46 (bs, 1H), 7.98 (b, 1H), 7.80 (s, 1H), 7.64 (d, 1H, 8Hz), 7.30-7.42 (m, 5H), 6.87 (d, 1H, 8Hz), 6.45 (s,1H), 4.50 (dd, 1H, 9Hz, 3Hz), 3.85 (t, 2H, 6 Hz), 3.15 (dd, 1H, 18Hz, 4Hz), 2.80 (dd, 1H, 18Hz, 9Hz), 1.75 (q, 2H, 6Hz), .92 (t, 3H, 6Hz). MS (FI-NEG): M-H]$^-$= 413. Anal.Calc. for $C_{21}H_{22}N_2O_5S$: C, 60.85, H, 5.35, N, 6.76. Found: C, 60.49, H, 5.31, N, 6.51.

Example 39

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl]-amino}-2-oxoethyl)-2-(4-propoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

{(2S*,5S*)-3-[3-(aminocarbonyl) phenyl]-2-[4-propoxyphenyl]-4-oxo-1,3-thiazolidin-5-yl} acetic acid (500 mg, 1.2 mmol) was dissolved in methanol (20 mL) and THF (20 mL) at 80°C. DBU (2.27 g, 15 mmol) was added, and the solution was allowed to stir for 15 hours. Analytical HPLC (isocratic, 45% acetonitrile/water) showed two components in a 65:35 ratio. The more abundant material proved upon co-injection to be the trans epimer. The solvent was removed under vacuum, and the oil remaining was partitioned between ethyl acetate and 3 N HCl. The ethyl acetate fraction was washed two additional times with acid. The organic layer was separated, washed with brine and dried using $MgSO_4$. The solvent was removed under reduced pressure, yielding a mixture of *cis*

and *trans* epimers as a white solid. A portion of this crude material (350 mg, .87 mmol) was dissolved in DMF (5 mL) with DIEA (120 mg, 1.0 mmol) and 3-ethoxy-4-methoxyphenethylamine (195 mg, 1.0 mmol). HATU (380 mg, 1.0 mmol) was added and the solution was allowed to stir at room temperature for 15 hours. The DMF solution was partitioned between ethyl acetate and brine twice, and the organic layer was washed twice with 3N HCl. The organic layer was washed again with brine and dried using $MgSO_4$. The solvent was removed under vacuum, yielding the crude products as a yellow oil. The mixture was purified using preparative HPLC (40 acetonitrile/water (.1% TFA)) to yield the *cis* title product (110 mg, 22%): ^{1}H NMR (DMSO-d_6): δ 8.15 (m, 1H), 7.92 (bs, 1H), 7.72 (s, 1H), 7.62 (d, 1H, 8Hz), 7.30-7.42 (m, 4H), 6.70-6.82 (m, 4H), 6.39 (s, 1H), 5.85 (s, 1H), 4.38 (dd, 1H, 9Hz, 3Hz), 3.99 (q, 2H, 8 Hz), 3.83 (t, 2H), 3.64 (s, 3H), 3.26 (m, 2H), 3.15 (dd, 1H, 18Hz, 4Hz), 2.80 (dd, 1H, 18 Hz, 9Hz), 2.62 (m, 2H), 1.75 (q, 2H, 6Hz), 1.32 (t, 3H, 8 Hz) .92 (t, 3H, 6Hz).. MS (ESI-NEG):[M-H]$^-$= 592. Anal.Calc. for $C_{32}H_{37}N_3O_6S$: C, 64.95, H, 6.30, N, 7.10. Found: C, 62.56, H, 6.33, N, 6.76.

Example 40

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl]amino}-2-oxoethyl)-2-(4-propoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

{(2S*,5S*)-3-[3-(aminocarbonyl) phenyl]-2-[4-propoxyphenyl]-4-oxo-1, 3-thiazolidin-5-yl} acetic acid (500 mg, 1.2 mmol) was dissolved in methanol (20 mL) and THF (20 mL) at 80°C. DBU (2.27 g, 15 mmol) was added, and the solution was allowed to stir for 15 hours. Analytical HPLC (isocratic, 45% acetonitrile/water) showed two components in a 65:35 ratio. The more abundant material proved upon co-injection to be the trans epimer. The solvent was removed under vacuum, and the oil remaining was partitioned between ethyl acetate and 3 N HCl. The ethyl acetate fraction was washed two additional times with acid. The organic layer was separated, washed with brine and dried using $MgSO_4$. The solvent was removed under reduced pressure, yielding a mixture of *cis* and *trans* epimers as a white solid. A portion of this crude material (350 mg, .87 mmol) was dissolved in DMF (5 mL) with DIEA (120 mg, 1.0 mmol) and 3-ethoxy-4-methoxyphenethylamine (195 mg, 1.0 mmol). HATU (380 mg, 1.0 mmol) was added and the solution was allowed to stir at room temperature for 15 hours. The DMF solution was partitioned between ethyl acetate and brine twice, and the organic layer was washed twice

with 3N HCl. The organic layer was washed again with brine and dried using $MgSO_4$. The solvent was removed under vacuum, yielding the crude products as a yellow oil. The mixture was purified using preparative HPLC (40 acetonitrile/water (.1% TFA)) to yield the *trans* title product (180 mg, 40%): ^1H NMR (DMSO-d_6): δ 8.15 (m, 1H), 7.92 (bs, 1H), 7.72 (s, 1H), 7.62 (d, 1H, 8Hz), 7.30-7.42 (m, 4H), 6.70-6.82 (m, 4H), 6.39 (s, 1H), 5.88 (s, 1H), 4.45 (m, 1H), 3.99 (q, 2H, 8 Hz), 3.83 (t, 2H), 3.64 (s, 3H), 3.26 (m, 2H), 3.15 (dd, 1H, 18Hz, 4Hz), 2.80 (dd, 1H, 18Hz, 9Hz), 2.62 (m, 2H), 1.75 (q, 2H, 6Hz), 1.32 (t, 3H, 8 Hz) 0.92 (t, 3H, 6Hz). MS (ESI-NEG): $[M-H]^-$= 592. Anal.Calc. for $C_{32}H_{37}N_3O_6S$: C, 64.95, H, 6.30, N, 7.10. Found: C, 63.82, H, 6.21, N, 7.06.

Example 41

Preparation of {(2S*,5S*)-3-[5-(aminocarbonyl) pyridin-2-yl]-2-[4-(benzyloxy) phenyl]-4-oxo-1,3-thiazolidin-5-yl} acetic acid.

A round-bottomed flask was fitted with a bump trap containing molecular sieves (8g, 4A). 6-Aminonicotimide (1.00g, 7.3 mmol) and 4-benzyloxybenzaldehyde (1.87g, 8.8 mmol). were allowed to stir in acetonitrile (60 mL) at 80°C for 1 hour. Mercaptosuccinic acid (3.3g, 22 mmol) was added to the reaction mixture. The solution was allowed to stir for 15 hours. The precipitate was filtered, yielding the predominantly *cis* title product (2.44g, 72%) as a white solid. ^1H NMR (DMSO-d_6): δ 8.85 (m, 1H), 8.29 (dd, 1H, 8 Hz, 2Hz), 8.15 (m, 1H), 8.03 (bs, 1H), 7.89 (d, 1H, 8 Hz), 7.58 (bs, 1H), 7.25-7.42 (m, 4H), 6.70-6.98 (m, 4H), 5.01 (s, 2H), 4.44 (dd, 1H, 9 Hz, 3Hz), 3.64 (s, 3H), 3.15 (dd, 1H, 18 Hz, 4Hz), 2.80 (dd, 1H, 18 Hz, 9Hz). MS (ESI-POS): $[M-H]^-$= 462. Anal.Calc.for $C_{35}H_{36}N_4O_6S$: C, 65.61, H, 5.66, N, 8.74. Found: C, 59.29, H, 5.13, N, 7.79.

Example 42

Preparation of 6-[(2S*,5S*ns)-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl] amino)-2-oxoethyl)-4-oxo-1,3-thiazolidin-3-yl} nicotinamide.

{(2S*,5S*)-3-[5-(aminocarbonyl) pyridin-2-yl]-2-[4-(benzyloxy) phenyl]-4-oxo-1, 3-thiazolidin-5-yl} acetic acid (1.0 g, 2.2 mmol) was dissolved in DMF (20 mL) with HATU (1.25 g, 3.3 mmol), 3-methoxy-4-ethoxy-phenethylamine (644 mg, 3.3 mmol) and DIEA (430 mg, 3.3 mmol). The mixture was allowed to stir for 15 hours under nitrogen, when it was found to be complete by tlc. The DMF solution was diluted with ethyl acetate, washed twice with brine and twice with 3N HCl solution. The organic layer

was filtered, yielding the title product (560 mg, 40%) as a white solid. ^{1}H NMR (DMSO-d_6): δ 8.85 (m, 1H), 8.29 (dd, 1H, dd, 8 Hz, 2 Hz), 8.15 (m, 1H), 8.03 (bs, 1H), 7.89 (d, 1H, 8 Hz), 7.58 (bs, 1H), 7.25-7.42 (m, 6H), 6.70-6.98 (m, 5H), 5.01 (s, 2H), 4.44 (dd, 1H, 9 Hz, 3Hz), 3.99 (q, 2H, 8 Hz), 3.64 (s, 3H), 3.60 (s, 3H), 3.26 (m, 2H), 3.15 (dd, 1H, 18Hz, 4Hz), 2.80 (dd, 1H, 18 Hz, 9Hz), 2.62 (m, 2H), 1.32 (t, 3H, 8 Hz). MS (ESI-POS): $[M+H]^+ = 564$. Anal.Calc. for $C_{35}H_{36}N_4O_6S$: C, 65.61, H, 5.66, N, 8.74. Found: C, 59.29, H, 5.13, N, 7.79.

Example 43

Preparation of N-[2-(3-ethoxy-4-methoxyphenyl)ethyl]-2,2,2,-trifluoroacetamide.

3-Methoxy-4-ethoxy-phenethylamine (10.0 g, 51 mmol) was dissolved in toluene (200mL) with DIEA (7.1 g, 55 mmol). This solution was treated with trifluoroacetic acid anhydride (12.9 g, 55 mmol). The solution was allowed to stir at room temperature for 2 hours. The solvent was removed under vacuum, and the residue was partitioned between ethyl acetate and water. The organic layer was washed three times with 3N HCl. It was dried with brine and magnesium sulfate. The solvent was removed by rotary evaporation to yield the title compound (11.6 g, 78%) as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 9.42 (m, 1H), 6.83 (d, 1H, 7 Hz), 6.78 (d, 1H, 1 Hz), 6.65 (dd, 1H, 7 Hz, 1Hz), 3.95 (q, 2H, 8 Hz), 3.72 (s, 3H), 3.38 (q, 2H, 6 Hz), 2.72 (t, 3H, 6 Hz), 1.34 (t, 3H, 8 Hz). MS (ESI-POS): $[M+H]^+ = 292$. Anal.Calc. for $C_{13}H_{16}F_3NO_3$: C, 53.61, H, 5.54, N, 4.81. Found: C, 51.90, H, 5.05, N, 4.54.

Example 44

Preparation of N-[2-(5-ethoxy-2-iodo-4-methoxyphenyl)ethyl]-2,2,2,-trifluroacetamide.

N-[2-(3-ethoxy-4-methoxyphenyl)ethyl]-2,2,2,-trifluoroacetamide (500 mg, 1.7 mmol) was dissolved in MeOH (16 mL). Iodine (765 mg, 3.0 mmol) was added. This solution was treated with HIO_3 (264 mg, 1.5 mmol, dissolved in17 mL of water). The reaction mixture was protected from light, and it was allowed to stir under nitrogen for 20 hours. The reaction mixture was partitioned between ethyl acetate and a weak sodium bisulfite solution. The ethyl acetate layer was washed one additional time with bisulfite, and then it was washed with bicarbonate. It was dried with brine and magnesium sulfate, and concentrated under vacuum yielding the title product (575 mg, 81%). ^{1}H NMR

(DMSO-d_6): δ 9.48 (m, 1H), 7.24 (s, 1H), 6.88 (s, 1H), 3.99 (q, 2H, 8 Hz), 3.72 (s, 3H), 3.38 (q, 2H, 6 Hz), 2.72 (t, 3H, 6 Hz), 1.34 (t, 3H, 8 Hz). MS (ESI-NEG):$[M-H]^-$= 416. Anal.Calc. for $C_{13}H_{15}F_3INO_3$: C, 37.43, H, 3.62, N, 3.18. Found: C, 36.76, H, 3.43, N, 3.18.

Example 45

Preparation of 2-(5-ethoxy-2-iodo-4-methoxy-phenyl)-ethylamine.

N-[2-(5-Ethoxy-2-iodo-4-methoxyphenyl)ethyl]-2,2,2,-trifluroacetamide (2.0 g, 4.8 mmol) was stirred in MeOH (60 mL) and water (20 mL). Lithium hydroxide monohydrate (1.05 g, 25 mmol) was added and the mixture was heated to 60°C and allowed to stir for 1 hour. The reaction mixture was diluted with ethyl acetate, and washed three times with water. It was dried using brine and magnesium sulfate, and concentrated under vacuum to yield the title compound (1.4 g, 89%). ^1H NMR (DMSO-d_6): δ 7.27 (s, 1H), 6.92 (s, 1H), 3.99 (q, 2H, 8 Hz), 3.72 (s, 3H), 3.38 (q, 2H, 6 Hz), 2.72 (t, 3H, 6 Hz), 1.34 (t, 3H, 8 Hz). MS (ESI-POS):$[M+H]^+$= 322. Anal.Calc. for $C_{11}H_{16}INO_2$: C, 41.14, H, 5.02, N, 4.36. Found: C, 40.36, H, 4.75, N, 3.75.

Example 46

Preparation of 3-[(2S*,5R*)-5-(2-{[2-(5-ethoxy-2-iodo-4-methoxyphenyl)ethyl]amino}-2-oxoethyl)-2-(4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

[(2S*,5R*)-3-[3-(Aminocarbonyl) phenyl]-2-(4-(hydroxyphenyl)-4-oxo-1,3-thiazolidin-5-yl] acetic acid (240 mg, .65 mmol) was dissolved in DMF (6 mL) with HATU (296 mg, .78 mmol), 2-(5-ethoxy-2-iodo-4-methoxy-phenyl)-ethylamine (250 mg, .78 mmol) and DIEA (100 mg, .78 mmol).The solution was allowed to stir for 2 hours. The DMF solution was diluted with ethyl acetate, washed twice with brine, and twice with 3N HCl. The ethyl acetate was dried over MgSO4, and concentrated by rotary evaporation. This crude was purified using silica gel column chromatography (6% MeOH/DCM) to yield the product (110mg, 25%) as yellow solid. ^1H NMR (DMSO-d_6): δ 9.54 (s, 1H), 8.15 (m, 1H), 7.92 (bs, 1H), 7.72 (s, 1H), 7.62 (d, 1H, 8 Hz), 7.30-7.42 (m, 3H), 7.25 (d, 1H, 9 Hz), 6.70-6.82 (m, 3H), 6.69 (d, 1H, 8 Hz), 6.35 (s, 1H), 4.44 (dd, 1H, 9 Hz, 3 Hz), 3.89 (q, 2H, 8 Hz), 3.64 (s, 3H), 3.26 (m, 2H), 3.15 (dd, 1H, 18 Hz, 4 Hz), 2.80 (dd, 1H, 18 Hz, 9 Hz), 2.62 (m, 2H),1.32 (t, 3H, 8 Hz). MS (ESI-POS):$[M+H]^+$=

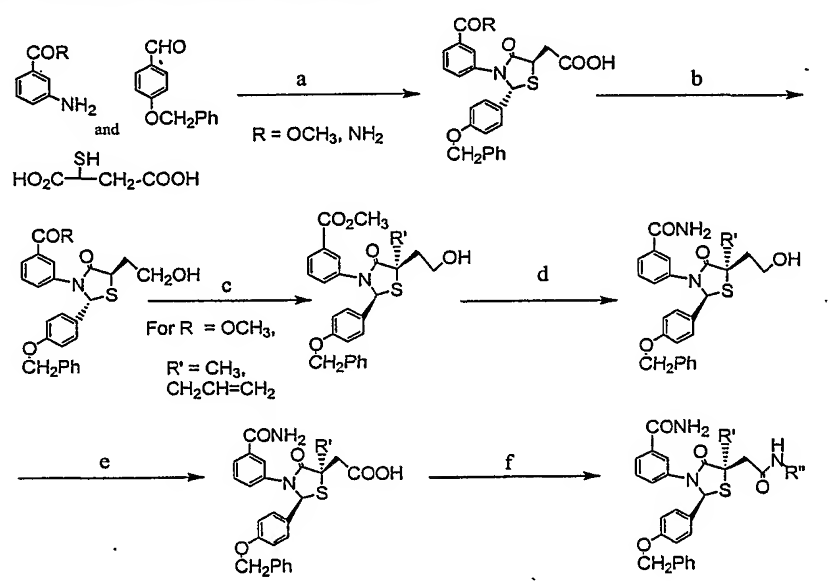
676. Anal.Calc. for $C_{29}H_{30}IN_3O_6S$: C, 63.37, H, 5.68, N, 7.64. Found: C, 61.57, H, 6.19, N, 6.87.

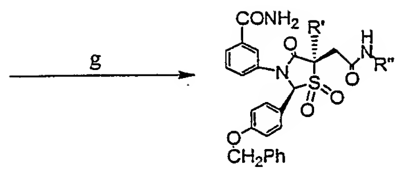
Example 47

Preparation of 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(5-ethoxy-2-iodo-4-methoxyphenyl) ethyl]amino}-2-oxoethyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide.

3-[(2S*,5R*)-5-(2-{[2-(5-Ethoxy-2-iodo-4-methoxyphenyl)ethyl]amino}-2-oxoethyl)-2-(4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide (63 mg, .090 mmol) was dissolved in DMF (1.5 mL) with benzyl bromide (34 mg, .2 mmol). Potassium carbonate (28 mg, .2 mmol, dissolved in .5 mL of water) was added. The reaction mixture was allowed to stir under nitrogen for 24 hours. The DMF solution was partitioned between ethyl acetate and brine twice, and the organic layer dried using magnesium sulfate. The solvent was removed under vacuum. The crude material was purified using silica gel flash chromotography (4 % methanol:DCM), yielding the title compound (20 mg, 28%) as a yellow oil. ^1H NMR (DMSO-d_6): δ 8.15 (m, 1H), 7.92 (bs, 1H), 7.72 (s, 1H), 7.66 (d, 1H, 8 Hz), 7.30-7.56 (m, 10H), 7.25 (s, 1H), 6.80-6.92 (m, 3H), 6.69 (s, 1H), 6.35 (s, 1H), 5.01 (s, 2H), 4.44 (m, 1H), 3.95 (m, 2H), 3.74 (s, 3H), 3.26 (m, 2H), 3.15 (dd, 1H, 18 Hz, 4 Hz), 2.80 (dd, 1H, 18 Hz, 9 Hz), 2.62 (m, 2H),1.32 (t, 3H, 8 Hz). MS (ESI-POS):$[M+H]^+$ = 766. Anal.Calc. for $C_{36}H_{36}IN_3O_6S$: C, 56.47, H, 4.74, N, 5.49. Found: C, 55.89, H, 4.95, N, 5.21.

Scheme 4. For Examples 48-50, 61-63, 68-75.





a) CH_3CN, mole. sieves 4A, 80^{0}C; **b)** BOP, DIEA, THF for 6 hrs then reduced with 1.15 eq $NaBH_4$; **c)** LiCl, $LiTMS_2$, RX, -78^{0}C to -40^{0}C; **d)** NH_4OH, CH_3OH; **e)** Jones oxidation, 0^{0}C; **f)** RNH_2, HATU, DIAE, DMF, g) MCPBA, NMP, 60^{0}C.

Example 48

Preparation of [(2S*,5S*)-3-[3-(methoxycarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl]acetic acid.

At room temperature under N_2, methyl 3-aminobenzoate (18.12 g, 119.865 mmol), 4-benzyloxybenzaldehyde (25.44 g, 119.865 mmol), and mercaptosuccinic acid (27.00 g, 179.798 mmol) in acetonitrile (200 ml) was heated at reflux for 4 days. The resulting brown solution was concentrated *in vacuuo*. The brown syrup was partitioned between water and CH_2Cl_2 (400 ml, ea), extraction, separation, drying over $MgSO_4$ and concentration *in vacuuo* to a brown syrup. SiO_2 gravitational chromatography elution with Hexane : EtOAc (3:1, 2L), (2:1, 2L), (1:1, 4L), (1:1.5, 2L) afforded an orange powder (48.57 g, 85% yield). ^{1}H NMR (DMSO-d_6) δ 2.93 (dd, J = 8.37, 8.38 Hz, 1H), 3.04 (dd, J = 17.26, 3.95 Hz, 1H), 3.83 (s, 3H), 4.51 (ddd, J = 5.42, 3.94, 1.48 Hz, 1H), 5.00 (s, 2H), 6.47 (d, J = 1.48 Hz, 1H), 6.90 (d, J = 8 87 Hz, 2H), 7.31 (d, J = 6.90 Hz, 1H), 7.34 (m, 6H), 7.43 (t, J = 7.88 Hz, 1H), 7.53 (dd, J = 7.89, 0.99 Hz, 1H), 7.73 (d, J = 7.89 Hz, 1H), 7.94 (t, J = 1.48 Hz, 1H), 12.66 (s broad, 1H). MS (ESI) $[M+H]^-$ 476.

Example 49

Preparation of methyl 3-[(2S*,5S*)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-4-oxo-1,3-thiazolidin-3-yl]benzoate.

At room temperature under N_2 [(2S*,5S*)-3-[3-(methoxycarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl]acetic acid. (4.90 g, 10.277 mmol) in THF (200 ml), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (5.0 g, 11.305 mmol) and diisopropylethylamine (2.33 ml, 13.360 mmol) were added and stirred 6 hours. After the reagents were added, the initial yellow solution turned brown. The brown solution was cooled to 0° C upon which $NaBH_4$ (450 mg, 11.819 mmol) was added. Gas evolution persisted for about ½ hour, after which the

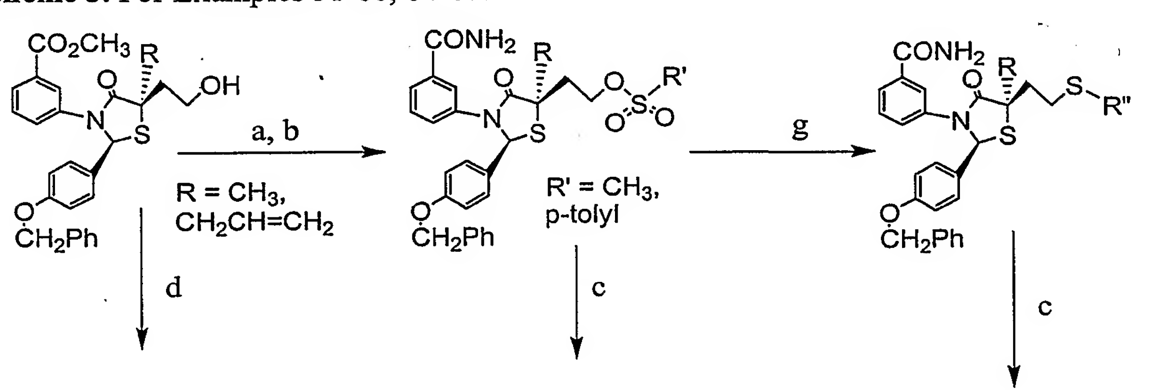
slightly cloudy brown solution with gradual warming to room temperature was stirred for 60 hours. To the resulting dark brown solution, concentration *in vacuo* to a brown syrup. Partition between EtOAc and cold 2N HCl_{aq} (250 ml ea) extraction, separation. Extraction of the aqueous layer with EtOAc (2 X 100 ml). All organic layers combined extraction with cold saturated $NaHCO_3$ $_{aq}$ (200 ml), water (150 ml), brine (100 ml), dried over $MgSO_4$, filtered, and concentration *in vacuo* to a brown syrup. Biotage SiO_2 chromatography (40M cartage) , 3:1 / Hex:EtOAc (1 L), 2:1 / Hex:EtOAc (3 L) afforded the title compound as a light brown powder (2.81 g , 63% yield). ^{1}H NMR (DMSO-d_6) δ 1.17 (m, 1H), 2.22 (m, 1H), 3.53 (m, 1H), 3.64 (m, 1H), 3.83 (s, 3H), 4.32 (dd, J = 4.02, 0.72 Hz, 1H), 4.72 (t, J = 5.13 Hz, 1H), 5.01 (s, 2H), 6.55 (s, 1H), 6.88 (q,d, J = 8.79, 1.83 Hz, 2H), 7.30 (m, 7H), 7.43 (t, J = 8.05 Hz, 1H), 7.55 (dd, J = 6.95, 1.10 Hz, 1H), 7.12 (d, J = 8.06 Hz, 1H), 7.95 (t, J = 2.20 Hz, 1H). MS (ESI) $[M+H]^+$ 464. Anal. RP-HPLC 75%.

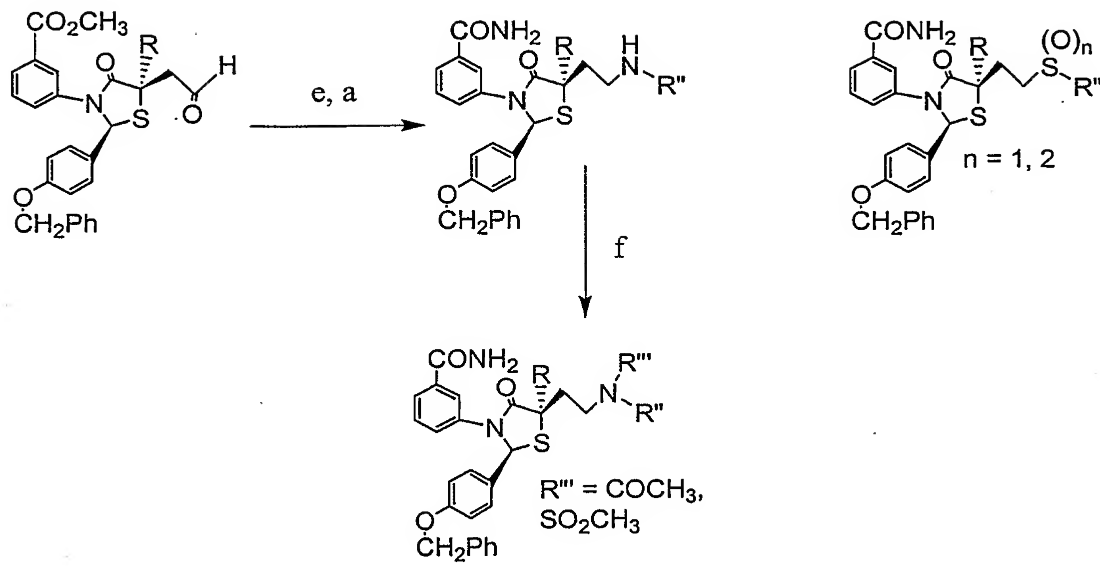
Example 50

Preparation of 3-[(2S*,5S*)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide.

Prepared according to the procedure in the above example starting from {(2S*,5S*)-3-[3-(aminocarbonyl) phenyl]-2-[4-(benzyloxy) phenyl]-4-oxo-1,3-thiazolidin-5-yl} acetic acid (5.57 g, 11.664 mmol) afforded the title compound as a brown powder (1.78 g, 35% Yield). MS (ESI) $[M+H]^+$ 449.

Scheme 5. For Examples 51-60, 64-67.





a) NH_4OH, CH_3OH; **b)** $R'SO_2Cl$, pyridine, 0^0C; **c)** $R''NH_2$, benzene, reflux; **d)** Jones oxidition, 0^0C; **e)** $R''NH_2$, $NaBH(OAc)_3$, HOAc, CH_2Cl_2, rt; **f)** AcCl or CH_3SO_2Cl, Cs_2CO_2, DMF, rt; **g)** $(R''S)_2$, $NaBH_4$, DMF, 55^0C; **h)** H_2O_2, H_2O, HOAc, 0^0C for n = 1, H_2O_2, acetone, 45^0C for n = 2.

Example 51

Preparation of 2-{(2S*,5S*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl}ethyl 4-methylbenzenesulfonate.

3-[(2S*,5S*)-2-[4-(Benzyloxy)phenyl]-5-(2-hydroxyethyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide (500 mg, 1.1 mmol) in pyridine (20 ml) was cooled to 0^0 C/N_2 and treated with tosyl chloride (381 mg, 2 mmol). The resulting solution was stirred at rt/N_2 for 18 hours. The solvent was evaporated at 40^0 under reduced pressure, the residue was treated with water (25 ml) and acidified with aqueous 2N HCl. The acidic solution was extracted with ethyl acetate (5 x 40 ml). The ethyl acetate solution was washed with water, dried with $MgSO_4$ and evaporated. Chromatography of the crude product on silica gel and elution with 2 % methanol in CH_2Cl_2 afforded 175 mg (26 % yield) of the title compound as a white solid; ^{1}HNMR (DMSO-d_6) δ 8.0-6.8 (m, 17 H), 6.44 (s, 1 H), 5.00 (s, 2H), 4.20 (m, 3H), 2.42 (s, 3H), 2.40, 2.13 (mm, 2H); MS (ES-positive): $[M+H]^+$ 603.

Example 52

Preparation of 2-{(2S*,5S*)-3-[3-(amino-carbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl}ethyl methane-sulfonate.

Using the same procedure as in the above example except using 690 mg 3-[(2S*,5S*)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide, 408 mg methanesulfonyl chloride, 15 ml pyridine and all the other reagents scaled to this proportion afforded 500 mg (63 % yield) of the title compound. MS (ES-positive): $[M+H]^+$ 527.

Example 53

Preparation of 3-[(2S*,5S*)-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxy-phenyl)ethyl]amino}ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide.

At rt/N_2, {(2S*,5S*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl}ethyl 4-methylbenzenesulfonate (410 mg,0.68 mmol) was dissolved in benzene (10 ml) and treated with 3-ethoxy-4-methoxyphenethylamine (288 mg, 2.72 mmol). After refluxing under N_2 for 9 hours, the solution was evaporated and the residue was further dried at 70^0 C in vacuum for 8 hours. The gummy residue was dissolved in CH_2Cl_2 (200 ml), washed with water (2 x 25 ml), dried over anhydrous K_2CO_3 and evaporated. Chromatography of the crude product on silica gel and elution with 2.5 % methanol in CH_2Cl_2 afforded 170 mg (35 % yield) of the title compound as a white foam; ^{1}HNMR: (DMSO-d_6) δ 8.0-6.6 (m, 16 H), 6.46 (s, 1 H), 5.01 (s, 2H), 4.34 (m, 1 H), 3.96 (m, 2H), 3.70 (s, 3H), 1.29 (m, 3H); MS (ES-positive): $[M+H]^+$ 626.

Example 54

Preparation of 3-[2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3,4-dimethoxyphenyl)ethyl]amino}-ethyl)-4-oxo-1.3-thiazolidin-3-yl]benzamide.

(2-{(2S*,5S*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl}ethyl methanesulfonate (5.0 g, 9.5 mmol) was suspended in benzene (180 ml) and was treated with 3,4-dimethoxyphenethylamine (5.5 g, 28.5 mmol). The mixture was heated under reflux /N_2 for 6.5 hours. Benzene was removed by evaporation, the residue was diluted with CH_2Cl_2 (900 ml), washed with water (7 x 120 ml), dried and evaporated to give an oil (8.5 g). This oil was dissolved in THF (150 ml), treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (20 ml, 118 mmol) and heated at reflux/N_2 for 20 hours. The reaction mixture was diluted with CH_2Cl_2 (1 l), washed with water (10 x 120 ml), dried with $MgSO_4$ and evaporated. Chromatography of the crude product on silica gel and elution with 4.5 % methanol in CH_2Cl_2 afforded 1.7 g (30 %

yield for the two-step reaction) of the title compound as a pale white solid; ^{1}HNMR (DMSO-d_6) δ 7.9-6.6 (m, 16 H), 6.47, 6.46 (ss, 1H, cis/trans isomeric ratio about 1/1), 5.01, 4.99 (2s, 2H, cis/trans isomeric ratio about 1/1), 4.34, 4.23 (2m, 1H, cis/trans isomeric ratio about 1/1), 3.71, 3.70 (2s, 3H each); MS (ES-positive): $[M+H]^+$ 612; Anal. Calc. For $C_{35}H_{37}N_3O_5S$ 1/2 H_2O: C,67.71. H,6.17. N,6.76. Found: C,67.40. H,6.454. N,6.75.; Analytical HPLC determined that this compound 99 % purity consisted cis/trans isomeric ratio 46/54.

This compound (0.9 g, 1.45 mmol) was dissolved in a solution of ethyl acetate (10 ml)/ethyl ether (2 ml) and cooled to 0^0 C/ N_2. To the solution 1 M $HCl_{(gas)}$ in ether (1.5 ml) was added at 0^0 C/N_2 and a crystalline material was formed immediately. The resulting suspension was stirred at 0^0 C/N_2 for 2 hours. The crystalline material was collected by filtration, dried at in vacuum to afford 0.89 g (90 % yield) of the hydrochloride salt of the title compound as a pale white form; ^{1}HNMR (DMSO-d_6) δ 8.0-6.7 (m, 16 H), 6.56, 6.53 (2s, 1H, cis/trans isomeric ratio about 1/1), 5.01, 5.00 (2s, 2H, cis/trans isomeric ratio about 1/1), 4.51, 4.38 (mm, 1H, cis/trans isomeric ratio about 1/1), 3.75, 3.72 (2s, 3H each); MS (ES-positive): $[M+H]^+$ 612; Analytical HPLC determined that this compound 99 % purity consisted cis/trans isomeric ratio 46/54.

Example 55

Preparation of 3-[2-[4-(benzyloxy)phenyl]-5-(2-{[2-(4-ethoxy-3-methoxyphenyl)ethyl]amino}ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide.

Using the procedure of the above example except using 700 mg (2-{(2S*,5S*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl}ethyl methanesulfonate), 780 mg 4-ethoxy-3-methoxy-phenethylamine, and 25 ml of benzene afforded 170 mg (30 % yield) of the title compound; MS (ES- positive): $[M+H]^+$ 626.

Example 56

Preparation of 3-{5-(2-{acetyl [2-(3,4-dimethoxyphenyl)ethyl]-amino)ethyl)-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolindin-3-yl)benzamide.

At rt/N_2 [2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3,4-dimethoxyphenyl)ethyl]-amino}ethyl)-4-oxo-1.3-thiazolidin-3-yl]benzamide (100 mg, 0.16 mmol) in DMF (2 ml) was treated with cesium carbonate (212 mg, 0.64 mmol). Acetyl chloride (50 mg, 0.64 mmol) in DMF (0.5 ml) was added and the suspension was stirred at rt/N_2 for 40 hours. It

was diluted with CH_2Cl_2 (200 ml), washed with water, dried with $MgSO_4$ and evaporated. Chromatography of the crude product on silica gel and elution with 2 % methanol in CH_2Cl_2 afforded 62 mg (58 % yield) of the title compound as a pale white form; ^{1}HNMR (DMSO-d_6): δ 7.9-6.6 (m, 16H), 6.45 (2s, 1H, cis/trans isomeric ratio about 1/1), 5.00, 4.98 (2s, 2H, cis/trans isomeric ratio about 1/1) 4.35-4.22 (m,1H), 3.70 (s, 6H), 1.86, 1.84 (2s, 3 H).; MS (ES-positive): $[M+H]^+$ 654; Analytical HPLC determined that this compound 96 % purity consisted cis/trans isomeric ratio 46/50.

Example 57

Preparation of 3-(2-[4-(benzyloxy)phenyl]-5-{2-[[2-(3,4-dimethoxyphenyl)ethyl]-(methylsulfonyl)amino]ethyl}-4-oxo-1,3-thiazolindin-3-yl)benzamide.

At rt/N_2 3-[2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3,4-dimethoxyphenyl)ethyl]amino}ethyl)-4-oxo-1.3-thiazolidin-3-yl]benzamide (100 mg, 0.16 mmol) in DMF (2 ml) was treated with cesium carbonate (212 mg, 0.64 mmol). To the suspension at 0^0 C/N_2 methanesulfonyl chloride (73 mg, 0.64 mmol) in DMF (0.5 ml) was added and stirred at rt/N_2 for 20 hours. It was diluted with CH_2Cl_2 (200 ml), washed with water, dried with $MgSO_4$ and evaporated. Chromatography of the crude product on silica gel and elution with 2.5 % methanol in CH_2Cl_2 afforded the title compound 56 mg (50 % yield) as a pale white form; ^{1}HNMR (DMSO-d_6): δ 8.0-6.7 (m, 16H), 6.50, 6.47 (2s, 1H, cis/trans isomeric ratio about 1/1), 5.00, 4.98 (2s, 2H, cis/trans isomeric ratio about 1/1) 4.30, 4.27 (mm,1H, cis/trans isomeric ratio about 1/1), 3.73, 3.72, 3.71, (3s, 3H each); MS (ES-positive): $[M+H]^+$ 690; Analytical HPLC determined that this compound 99 % purity consisted cis/trans isomeric ratio 48/52.

Example 58

Preparation of 3-[2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3,4-dimethoxyphenyl)ethyl] thio}ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide.

At room temperature under N_2, 3,4-dimethoxyphenethyl alcohol (2.00g, 10.976 mmol) in $CHCl_3$ (30 ml) was added pyridine (1.74g, 21.951 mmol) and methanesulfonyl chloride (1.63g, 14.269 mmol). The resulting yellow solution was stirred at room temperature for 63 hrs. The yellow solution was partitioned with 2N HCl_{aq} (3 X 50 ml), extraction, separation, drying over $MgSO_4$, filtration and concentration *in vacuuo* provided, as a pale syrup, 3,4-dimethoxyphenethyl methanesulfonate (2.46g, 86% yield).

^1H NMR (DMSO-d_6) δ 2.90 (t, J = 6.90 Hz, 2H), 3.11 (s, 3H), 3.72 (s, 3H), 3.75 (s, 3H), 4.36 (t, J = 6.90 Hz, 2H), 6.78 (dd, J = 8.13, 1.78 Hz, 1H), 6.87 (d, J = 8.13 Hz, 1H), 6.91 (d, J = 1.78 Hz, 1H). MS (ESI) $[M+Na]^+$ 283.

At room temperature under N_2, a solution of this compound (1.78g, 6.838 mmol) in DMF (25 ml) was degassed three times *in vacuuo* and vacuum replaced with N_2. Upon which, sodium hydrosulfide mono-hydrate (460 mg, 8.206 mmol) was added producing a blue mixture. The blue mixture was stirred at room temperature for 63 hrs. The resulting white mixture was quenched with 2N HCl_{aq} (20 ml). Partition between water (20 ml) and EtOAc (30 ml), extraction, separation. Extraction of the organic layer with water (3 x 15 ml), brine (15 ml), dried over $MgSO_4$, filtration and concentration *in vacuuo* to a brown syrup. Gravitional SiO_2 chromatography (6:1 / Hex: EtOAc) afforded a yellow syrup (780 mg, 55% yield) as 3,4-dimethoxyphenethyl thiol. ^1H NMR (DMSO-d_6) δ 1.55 (t, J = 7.65 Hz, 1H), 2.70 (t, J = 7.65 Hz, 2H), 2.71 (t, J = 7.65 Hz, 2H), 3.75 (s, 3H), 3.77 (s, 3H), 6.71 (dd, J = 8.13, 1.78 Hz, 1H), 6.80 (d, J = 8.13 Hz, 1H), 6.83 (d, J = 1.78 Hz, 1H). MS (ESI) $[M+dimer-2H]^+$ 394.

At room temperature under N_2, a solution of this compound (370 mg, 1.866 mmol) in DMF (10 ml) was degassed three times *in vacuuo* and the vacuum replaced with N_2. To the yellow solution, sodium hydride (81 mg, 2.022 mmol) was added producing an initial gray mixture, which was stirred 30 min that eventually turned into a yellow solution. 2-{3-[3-(Amino-carbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl}ethyl methane-sulfonate (818 mg, 1.555 mmol) in DMF (5 ml) was heated at 55°C upon which sodium 3,4-dimethoxyphenethyl thiol in DMF (10.5 ml) was added dropwise over 20 min period. The resulting brown solution was heated at 55°C for 6 hrs. Cooling of the dark brown solution to room temperature and quenching with 2N HCl_{aq} (20 ml). Partition of the aqueaous solution with EtOAc (20 ml) extraction, separation. Extraction and separation of the aqueous layer with EtOAc (10 ml). All organic layers were combined, extraction with water (2 X 15 ml), brine (15 ml), dried over $MgSO_4$, filtration, and concentration *in vacuuo* to a brown syrup. Gravitational SiO_2 chromatography 4% MeOH : CH_2Cl_2 afforded the title compound as a yellow foam (460 mg, 47% yield) of trans 3-[2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3,4-dimethoxyphenyl)ethyl] thio}ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide. ^1H NMR (DMSO-d_6) δ 2.07 (m, 1H), 2.27 (m, 1H), 2.67 (m, 6H), 3.69 (s, 3H), 3.70 (s, 3H), 4.40 (dd, J = 7.79, 4.13 Hz, 1H),

5.01 (s, 2H), 6.51 (s, 1H), 6.71 (dd, J = 8.12, 1.83 Hz, 1H), 6.82 (m, 3H), 7.30 (m, 9H), 7.64 (d, J = 7.52 Hz, 1H), 7.86 (s, 1H), 7.94 (d, J = 3.53 Hz, 1H). MS (ESI) $[M+H\}^+$ 629. This compound was epimerized using DBU in refluxing THF to afford the title compound as a pale white powder (130 mg, 76% yield). MS (ESI) $[M+H]^+$ 629. Anal. RP-HPLC 90% purity, 80% trans isomer, 20% cis isomer.

Example 59

Preparation of 3-[2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3,4-dimethoxyphenyl) ethyl]sulfinyl}ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide.

At 0°C under N_2, 3-[2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3,4-dimethoxyphenyl) ethyl] thio}ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide (300 mg, 0.476 mmol) in water (2 ml), acetic acid (5 ml) followed by hydrogen peroxide (30% aqueous solution, 0.5 ml) were added. The resulting yellow solution was stirred at 0°C for 3 hrs. Quenching with DMSO (0.25 ml) and partition between CH_2Cl_2 and water (50 ml ea), extraction and separation. The organic phase was dried over $MgSO_4$, concentration *in vacuuo* to a yellow syrup. Gravitational SiO_2 chromatography 3% MeOH: CH_2Cl_2 (500 ml), 5% MeOH : CH_2Cl_2 (500 ml) afforded the title compound as a white foam (307 mg, 46% yield). ^1H NMR (DMSO-d_6) δ 2.14 (m, 1H), 2.34 (m, 1H), 2.71 (m, 7H), 3.67 (m, 1H), 3.71 (s, 3H), 3.74 (s, 3H), 4.43 (m, 1H), 5.01 (s, 2H), 6.55 (s, 1H), 6.76 (dd, J = 8.10, 1.79 Hz, 1H), 6.86 (m, 3H), 7.29 (m, 8H), 7.63 (d, J = 7.48 Hz, 1H), 7.86 (s, 1H), 7.97 (s broad, 2H). MS (ESI) $[M+H]^+$ 645. This compound was epimerized using DBU in refluxing THF to afford the title compound as a yellow foam (107 mg, 76% yield). MS (ESI) $[M+H]^+$ 645. Anal. RP-HPLC 75% purity, trans isomer 46%, cis isomer 54%.

Example 60

Preparation of 3-[2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3,4-dimethoxyphenyl)ethyl] sulfonyl}ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide.

At room temperature under N_2, 3-[2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3,4-dimethoxyphenyl) ethyl] thio}ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide (130 mg, 0.207 mmol) in acetone (15 ml), hydrogen peroxide (30% aqueous solution, 15ml) was added. The resulting yellow solution was heated at 45°C for 48 hrs. Cooling to room temperature and quenching with DMSO (4 ml) followed by partition between water and CH_2Cl_2 (50 ml ea). Extraction, separation of the organic layer, drying over $MgSO_4$, filtration and concentration *in vacuuo* to a brown syrup. Gravitational SiO_2 chromatography 4%

MeOH: CH_2Cl_2 afforded the title compound as a yellow powder (40 mg, 29% yield). ^{1}H NMR (DMSO-d_6) δ 2.09 (m, 1H), 2.83 (m, 7H), 3.71 (s, 3H), 3.73 (s, 3H), 4.28 (m, 1H), 5.09 (s, 2H), 6.58 (s, 1H), 6.73 (d, J = 8.17 Hz, 1H), 6.85 (m, 2H), 7.06 (d, J = 8.71 Hz, 2H), 7.32 (m, 9H), 7.61 (dd, J = 7.90, 1.47 Hz, 1H), 7.72 (d, J = 7.73 Hz, 1H), 7.99 (m broad, 2H). MS (ESI) $[M+H]^-$ 659. This compound was epimerized using DBU in refluxing THF to afford the title compound as a yellow foam (20.4 mg, 50% yield), cis: trans mixture 20: 80 ratio. MS (ESI) $[M+H]^+$ 659. Anal. RP-HPLC 84%, 85% trans isomer, 8% cis isomer.

Example 61

Preparation of methyl 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate.

To THF (100 ml) at 0°C under N_2, n-butyl lithium (48.37 ml, 120.917 mmol, 2.0 M solution in hexane) was added by syringe and stirred 5 min.. To the pale yellow solution was added 1,1,1,3,3,3-hexamethyl disilazane (32.00 g, 115.66 mmol) over 3 min. producing gas evolution. The resulting colorless solution was stirred at 0°C for 25 min. To methyl 3-[(2S*,5S*)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-4-oxo-1,3-thiazolidin-3-yl]benzoate (24.27 g, 52.573 mmol), lithium chloride (8.91 g, 210.290 mmol) in THF (350 ml) at -45°C, was added lithium 1,1,1,3,3,3,-hexamethyldisilazane in THF (182 ml solution) at a rate where the reaction temperature was -45°C +/- 3°C (about 4 min.). The resulting dark brown mixture was stirred at -78°C for 3.5 hrs. To the dark brown solution, was added iodomethane (7.18 g, 262.863 mmol) and stirred at -78°C for 2.5 hrs. The resulting dark purple solution was warmed to -40°C upon which was quenched with saturated NH_4Cl_{aq} (500 ml). The resulting brown solution was partitioned with EtOAc (500 ml), extraction, and separation. The aqueous layer was extracted with EtOAc (500 ml). All organic layers were combined, washed with brine (300 ml), dried over $MgSO_4$, filtration and concentration *in vacuuo* to a dark brown syrup. Biotage Flash-75 (75-L cartridge) elution schedule: hexane : EtOAc / 3:1 (16L), 2:1 (12L), 1:1 (16L), 0:1 (8L). Collection of the clean fractions afforded a yellow foam (9.71 g, 39% yield) of the title compound and recovered starting material (12.18 g). ^{1}H NMR (DMSO-d_6) δ 1.63 (s, 3H), 1.99 (dd, J = 7.53, 2.38 Hz, 1H), 2.19 (qd, J = 2.78, 0.50 Hz, 1H), 3.65 (m, 1H), 3.73 (m, 1H), 3.83 (s, 3H), 4.69 (s broad, 1H), 4.99 (s, 2H), 6.60 (s, 1H), 6.87 (qd, J = 8.73, 1.10 Hz, 2H), 7.31 (m, 7H), 7.41 (t, J = 7.94 Hz, 1H), 7.54 (dq, J = 7.93, 1.20 Hz, 1H),

7.70 (dt, J = 7.93, 1.20 Hz, 1H), 7.90 (t, J = 1.99 Hz, 1H). MS (ESI) $[M+H]^+$ 478. Anal. RP-HPLC 92%.

Example 62

Preparation of methyl 3-[(2S*,5R*)-5-allyl-2-[4-(benzyloxy)phenyl]-5-(2-hydroxy ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzoate.

Using the procedure of the above example except using allyl bromide as the alkylating agent afforded the title compound as a yellow powder (790 mg, 36% yield). MS (ESI) $[M+H]^+$ 504.

Example 63

Preparation of 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide.

At room temperature in a coated flask opened to the atmosphere, methyl 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate (1.00 g, 2.094 mmol) in methyl alcohol (15 ml) was added ammonium hydroxide (20 ml, 30% aqueous solution). The resulting brown cloudy mixture was sealed with a teflon screw capped and stirred 4 days. To the yellow solution, concentration *in vacuuo* to a brown syrup. Biotage SiO_2 chromatography (5% MeOH: CH_2Cl_2) afforded the title compound as a yellow foam (640 mg, 66% yield). ^1H NMR (DMSO-d_6) δ 1.62 (s, 3H), 2.00 (qd, J = 8.02, 2.82 Hz, 1H), 2.16 (q, J = 8.02 Hz, 1H), 3.62 (m, 1H), 3.71 (m, 1H), 4.66 (t, J = 5.31 Hz, 1H), 4.99 (s, 2H), 6.51 (s, 2H), 6.87 (d, J = 8.85 Hz, 2H), 7.30 (m, 7H), 7.40 (dq, J = 7.78, 0.05 Hz, 2H), 7.63 (dt, J = 7.78, 1.41 Hz, 1H), 7.80 (t, J = 1.77 Hz, 1H), 7.93 (s broad, 2H). MS (ESI) $[M+H]^+$ 463. Anal. RP-HPLC 99% purity.

Example 64

Preparation of methanesulfonic acid 2-[(2S*,5R*)-2-(4-benzyloxy-phenyl)-3-(3-carbamoyl-phenyl)-5-methyl-4-oxo-thiazolidin-5-yl]-ethyl ester.

At 0°C under N_2, 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (200 mg, 0.433 mmol) in pyridine (5 ml) was added methanesulfonyl chloride (148 mg, 1.29 mmol) was added. The resulting red solution was stirred at 0°C for 2 hrs. The red solution was contated *in vacuuo* to a red syrup. Biotage SiO_2 chromatography 3% MeOH: CH_2Cl_2 afforded a yellow powder (130 mg, 56% yield). ^1H NMR (DMSO-d_6) δ 1.66 (s, 3H), 2.29 (m, 1H), 2.45 (m, 1H), 2.50 (s, 3H), 4.44 (m, 2H), 5.00 (s, 2H), 6.58 (s, 1H), 6.86 (d, J = 8.65 Hz,

2H), 7.32 (m, 6H), 7.44 (m, 2H), 7.63 (d, J = 7.68 Hz, 1H), 7.82 (s, 1H), 7.89 (s, 1H), 8.57 (s broad, 2H). MS (ESI) $[M+H]^+$ 541.

Example 65

Preparation of 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3,4-dimethoxy phenyl)ethyl]amino}ethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide.

At room temperature under N_2, methanesulfonic acid 2-[(2S*,5R*)-2-(4-benzyloxy-phenyl)-3-(3-carbamoyl-phenyl)-5-methyl-4-oxo-thiazolidin-5-yl]-ethyl ester (110 mg, 0.204 mmol) in DMF (10 ml), 3,4-dimethoxy phenethylamine (200 mg, 1.104 mmol) was added. The resulting yellow solution was heated at 75°C for 6 hrs. Concentration *in vacuo* to a brown syrup. Gravitational SiO_2 chromatography 4% MeOH: CH_2Cl_2 afforded the title compound as a yellow powder (80 mg, 63% yield). ^{1}H NMR (DMSO-d_6) δ 0.24 (s broad, 1H), 1.64 (s, 3H), 2.04 (m, 1H), 2.18 (m, 1H), 2.72 (m, 6H), 3.70 (s, 3H), 3.73 (s, 3H), 4.99 (s, 2H), 6.57 (s, 1H), 6.74 (dd, J = 8.11, 1.53 Hz, 1H), 6.84 (m, 4H), 7.28 (m, 9H), 7.63 (d, J = 7.56 Hz, 1H), 7.86 (s, 1H), 7.97 (s broad, 2H). MS (ESI) $[M+H]^+$ 626. Anal. RP-HPLC 89% purity.

Example 66

Preparation of 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3,4-dimethoxy phenyl)ethyl]thio}ethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide.

At room temperature under N_2, 3,4-dimethoxyphenethane thiol (97 mg, 0.489 mmol) in DMF (4 ml) was added sodium hydride (20 mg, 0.509 mmol) and stirred for 30 min.. At room temperature under N_2, methanesulfonic acid 2-[(2S*,5R*)-2-(4-benzyloxy-phenyl)-3-(3-carbamoyl-phenyl)-5-methyl-4-oxo-thiazolidin-5-yl]-ethyl ester (110 mg, 0.205 mmol) in DMF (30 ml) was added the sodium salt of 3,4-dimethoxyphenethane thiol in DMF (4 ml) and heated at 55°C for 3 hrs. Cooling of the resultant yellow solution to room temperature and quenching with 2N HCl_{aq} (50 ml). Partition with CH_2Cl_2 (40 ml) extraction, separation, drying over $MgSO_4$, filtration and concentration *in vacuo*. Biotage SiO_2 chromatography 2% MeOH: CH_2Cl_2 afforded the title compound as a yellow powder (410 mg, 19% yield). ^{1}H NMR (DMSO-d_6) δ 1.63 (s, 3H), 2.00 (m, 1H), 2.21 (m, 1H), 2.54 (m, 1H), 2.73 (m, 5H), 3.69 (s, 3H), 3.70 (s, 3H), 4.98 (s, 2H), 6.56 (s, 1H), 6.73 (dd, J = 8.18, 1.47 Hz, 1H), 6.83 (t, J = 9.93 Hz, 1H), MS (ESI) $[M+H]^+$ 643.

Example 67

Preparation of 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxy phenyl)ethyl]thio}ethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide.

Using the procedure of the above example and substituting 4-ethoxy-3-methoxyphenethane thiol for 3, 4-dimethoxyphenylethane thiol afforded the title compound as a yellow powder (220 mg, 62% yield). MS (ESI) $[M+H]^+$ 657.

Example 68

Preparation of 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxy phenyl)ethyl]amino}ethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide.

At 0 °C under N_2, CH_2Cl_2 (100 ml) was added pyridinium chlorochromate (4.51 g, 20.941 mmol). To the orange mixture was added methyl 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate (1.00 g, 2.094) in CH_2Cl_2 (60 ml) dropwise over 30 min.. The resulting dark brown mixture was stirred at 0°C 2 hrs. Quenching with water (150 ml), dilution with CH_2Cl_2 (100 ml), filtration through celite, extraction and separation. Extraction of the organic layer with water (2 X 150 ml), drying over $MgSO_4$, filtration and concentration *in vacuuo* to a dark brown syrup. Biotage SiO_2 chromatography (40s cartridge) 1:1 / Hex: EtOAc afforded methyl 3-[(2S*,5R*)-2-[4-(benzyloxy) phenyl]-5-(2-aldehylethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate as a yellow powder (617 mg, 62% yield). ^1H NMR (DMSO-d_6) δ 1.74 (s, 3H), 3.26 (s, 2H), 3.88 (s, 3H), 5.03 (s, 2H), 6.70 (s, 1H), 6.90 (d, J = 8.06, 2H), 7.35 (m, 7H), 7.46 (t, J = 8.06 Hz, 1H), 7.62 (d, J = 7.87 Hz, 1H), 7.76 (dd, J = 7.63, 0.78 Hz, 1H), 7.98 (s, 1H), 9.82 (s, 1H). MS (ESI) $[M+H]^+$ 476.

At room temperature under N_2, a solution of this aldehyde (100 mg, 0.210 mmol) in dichloroethane (5 ml) was added sodium triacetoxyborohydride (67 mg, 0.315 mmol), 3-ethoxy-4-methoxy phenethylamine (45 mg, 0.231 mmol) and glacial acetic acid (12 μL). The resulting yellow mixture was stirred at room temperature for 90 min. Quenching with saturated $NaHCO_{3\,aq}$ (10 ml), extraction, separation of the organic layer, dried over $MgSO_4$, filtration and concentration *in vacuuo* to a brown syrup. Biotage SiO_2 (40s) chromatography 3.5% MeOH : CH_2Cl_2 afforded methyl 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl]amino}ethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate as a brown powder (68 mg, 58% yield). ^1H NMR (DMSO-d_6) δ 1.26 (t, J = 6.95 Hz, 3H), 1.61 (s, 3H), 1.90 (m, 1H), 2.11 (m, 1H), 2.63 (m, 6H), 3.35 (s broad, 1H), 3.70 (s, 3H), 3.81 (s, 3H), 3.92 (q, J = 6.95 Hz, 2H), 4.98 (s, 2H),

6.59 (s, 1H), 6.69 (d, J = 8.09 Hz, 1H), 6.80 (m, 4H), 7.18 (m, 8H), 7.54 (d, J = 8.18 Hz, 1H), 7.69 (d, J = 7.69 Hz, 1H), 7.91 (s, 1H). MS (ESI) $[M+H]^+$ 655. This compound (250 mg, 0.382 mmol) was reacted with ammonia in methanol to afford the title compound as a yellow powder (110 mg, 45% yield). MS (ESI) $[M+H]^+$ 640. Anal. RP-HPLC 94% purity.

Example 69

Preparation of {(2S*,5R*)-2-[4-(benzyloxy)phenyl]-3-[3-(methoxycarbonyl)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}acetic acid.

Methyl 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate (160 mg, 0.32 mmol) was dissolved in acetone (16 ml) and cooled to -10^0 C/N_2. To the clear solution 1.4 M Jones reagent (0.4 ml) was added. The resulting mixture was stirred at -10^0 for 1.5 hours. It was treated with methanol (1ml), and 3 minutes later with saturated aqueous solution of sodium bicarbonate (2 ml) and 3 minutes later with acetic acid (1 ml) and filtered. After evaporation, the residue was diluted with water (15 ml) and extracted with CH_2Cl_2 (5x40 ml). The CH_2Cl_2 solution was washed with water, dried with $MgSO_4$ and evaporated. Chromatography of the crude product on silica gel and elution with 1 % methanol in CH_2Cl_2 afforded 70 mg (44 % yield) of the title compound as a foam; ^{1}HNMR ($CDCl_3$): δ 9.7 (broad, 1H), 7.9-6.7(m, 13H), 6.20 (s, 1H) 4.83 (s, 2H), 3.82 (s, 3H), 3.30, 3.00 (dd, J=16 Hz, 2H), 1.79 (s, 3H); MS (ES-positive): $[M+H]^+$ 492.

Example 70

{(2S*,5R*)-5-allyl-2-[4-(benzyloxy)phenyl]-3-[3-(methoxycarbonyl) phenyl]-4-oxo-1,3-thiazolidin-5-yl}acetic acid.

Using the procedure from the above example, methyl 3-[(2S*,5R*)-5-allyl-2-[4-(benzyloxy)phenyl]-5-(2-hydroxy ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzoate (400 mg, 0.794 mmol) was converted to the title compound: yellow foam (275 mg, 67% yield). MS (ESI) $[M+H]^+$ 518.

Example 71

Preparation of methyl 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxy-phenyl)ethyl]amino}-2-oxoethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate.

{(2S*,5R*)-2-[4-(Benzyloxy)phenyl]-3-[3-(methoxycarbonyl)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}acetic acid (240 mg, 0.49 mmol) was dissolved in DMF (15 ml) and was treated at rt/$N_2$with diisopropylethylamine (76 mg, 0.59 mmol) and 3-ethoxy-4-methoxyphenethylamine (114 mg, 0.59 mmol) in DMF (0.5 ml). To the solution at rt/N_2 O-(7-azabenzotriazole-1-yl)- N, N, N',N'-tetra-methyl uronium hexafluorphosphate (233 mg, 0.59 mmol) was added. The resulting solution was stirred at rt/N_2 for 20 hours. It was diluted with ethyl acetate (220 ml), washed with brine (3x20 ml), dried with $MgSO_4$ and evaporated. Chromatography of the crude product on silica gel and elution with 1.5 % methanol in CH_2Cl_2 afforded 250 mg (76 % yield) of the title compound as a white solid; ^{1}HNMR ($CDCl_3$): δ 7.9-6.6 (m, 16H), 6.17 (s, 1H) 4.95 (s, 2H), 4.04 (m, 2H), 3.87, 3.84 (ss, 3H each), 3.58, 3.50 (mm, 2H); MS (ES-positive): $[M+H]^+$ 669.

Example 72

Preparation of 3-[(2S*,5R*)-5-allyl-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl]amino}-2-oxoethyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide.

Using the procedure from the above example, {(2S*,5R*)-5-allyl-2-[4-(benzyloxy)phenyl]-3-[3-(methoxycarbonyl) phenyl]-4-oxo-1,3-thiazolidin-5-yl}acetic acid (230 mg, 0.444 mmol) afforded methyl 3-[(2S*,5R*)-5-allyl-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl]amino}-2-oxoethyl)-4-oxo-1,3-thiazolidin-3-yl]benzoate as a yellow powder (290 mg, 94% yield). MS (ESI) $[M+H]^+$ 695.

This compound (230 mg, 0.331 mmol) was stirred with ammonia in methanol to afford the title compound as a yellow syrup (190 mg, 84% yield). MS (ESI) $[M+H]^+$ 695.

Example 73

Preparation of {(2S*,5R*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}acetic acid.

3-[(2S*,5R*)-2-[4-(Benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (200 mg, 0.43 mmol) was dissolved in acetone (25 ml) and cooled to $-10^0/N_2$. To the solution 1.4 M Jones reagent (0.5 ml) was added over a period of 5 minutes. The orange mixture was stirred at -10^0 C for 2 hours. The mixture

was treated successionally with methanol (1 ml) and 3 minutes later with saturated aqueous solution of sodium bicarbonate (2 ml) and 3 minutes later with acetic acid (1 ml) and filtered. After evaporation the residue was diluted with water (15 ml) and extracted with CH_2Cl_2 (4x40 ml). The CH_2Cl_2 solution was washed with water, dried with $MgSO_4$ and evaporated. Chromatography of the crude product on silica gel and elution with 4 % methanol in CH_2Cl_2 afforded 100 mg (40 % yield) of the title compound as a white solid; ^{1}HNMR (DMSO-d_6): δ 8.0-6.8 (m, 13H), 6.51 (s, 1H) 4.99 (s, 2H), 3.07, 2.87 (dd, J=16 Hz, 2H), 1.67 (s, 3H, CH_3); MS (ES-positive): $[M+H]^+$ 477. Anal. Calc. For $C_{26}H_{24}N_2O_5S$. ½ H_2O: C,64.29. H,5.18. N,5.77. Found: C, 64.28. H, 5.27. N,5.58.

Example 74

Preparation of 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)-ethyl]amino}-2-oxoethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide.

{(2S*,5R*)-3-[3-(Aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}acetic acid (90 mg, 0.19 mmol) in DMF (7 ml) was treated at rt/N_2 with diisopropylethylamine (29.3 mg, 0.23 mmol), 3-ethoxy-4-methoxyphen-ethylamine (44.2 mg, 0.23 mmol) in DMF (0.5 ml) and O-(7-azabenzotriazol-l-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (86.2 mg, 0.23 mmol). After stirring at rt/N_2 for 20 hours, it was diluted with ethyl acetate (200 ml), washed with brine (3x 18 ml), dried with $MgSO_4$ and evaporated. Chromatography of the crude product on silica gel and elution with 3 % methanol in CH_2Cl_2 afforded 74 mg (60 % yield) of the title compound as a white powder; ^{1}HNMR (DMSO-d_6): δ 8.2-6.7 (m, 16H), 6.46 (s, 1H), 4.96 (s, 2H), 3.82 (m, 2H), 3.69 (s, 3H), 2.81(s, 2H), 2.63 (q, 2H), 1.57 (s, 3H); MS (ES-positive): $[M+H]^+$ 654.

Example 75

Preparation of 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxy-phenyl)ethyl]amino}-2-oxoethyl)-5-methyl-1,1-dioxido-4-oxo-1,3-thiazolidin-3-yl]benzamide.

3-[(2S*,5R*)-2-[4-(Benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)-ethyl]amino-2-oxoethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (770 mg, 1.18 mmol) was dissolved in 1-methyl-2-pyrrolidinone (20 ml) and treated with 3-chloroperoxy-benzoic acid (2 g, 60 %purity, 7 mmol). The resulting solution was

stirred at 60^0 C/N_2 for 2 days. All the solvent was removed at 60^0 under reduced pressure. The residue was dissolved in ethyl acetate (400 ml), washed with 10 % aqueous sodium sulfite solution (45 ml), saturated aqueous sodium bicarbonate solution (45 ml), brine and dried with $MgSO_4$. After evaporation of the solvent, the crude product was chromatographed on silica gel. Elution with 3 % methanol in CH_2Cl_2 afforded 695 mg (83 % yield) of the title compound as a white solid; ^{1}HNMR (DMSO-d_6): δ 8.24-6.71 (m, 16H), 6.80 (s, 1H) 5.02 (s, 2H), 3.97 (q, 2H), 3.71 (s, 3H), 3.30 (m, 2H), 2.97 (m, 2H), 2.64 (q, 2H), 1.67 (s, 3H), 1.29 (t, 3H); MS (ES-positive): $[M+H]^+$ 686.

Example 76

Preparation of 2-{(2S*, 5R*)-3-(3-acetylphenyl)-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl}-N-[2-(3-ethoxy-4-methoxyphenyl]ethyl]acetamide.

A solution of 3-aminoacetophenone (13.5 g, 100 mmol), 4-benzyloxybenzaldehyde (21.2 g, 100 mmol), and mercaptosuccinic acid (45 g, 300 mmol in acetonitrile (300 ml) was heated to reflux for 48 hours. The mixture was concentrated in vacuo. The residue was dissolved in methylene chloride, and the solution was washed with water, dried over magnesium sulfate, and concentrated. The residue was 2x triturated with ether, the combined ether extracts were dried and concentrated to afford crude product (8.5 g, 18 mmol). A solution of this product, and 1,8-diazabicyclo[5.4.0]undec-7-ene (5.6 g, 36 mmol) in acetonitrile (200 ml) was heated to reflux for 20 hours. The solution was concentrated in vacuo, and the residue was triturated with ethylacetate/1N hydrochloric acid. The solid crude product, a mixture of trans and cis isomer in a ratio 55/45 was collected by filtration and dried to afford [3-(3-acetylphenyl)-2-(4-benzyloxyphenyl)-4-oxo-1.3-thiazolidin-5-yl]acetic acid. (5.2 g, 61%), which was used without further purification.

A solution of this product (1.2 g, 2.6 mmol), 3-ethoxy-4-methoxyphenylethylamine (0.5 g, 26 mmol), diisopropylethylamine (0.4 g, 31 mmol), and O-(7-azabenzotriazol-1-yl)-N,N,N,N-tetramethyluronium (1 g, 26 mmol) in dimethylformamide (30 ml) was stirred at room temperature for 20 hours. The reaction mixture was diluted with water, and extracted with ethylacetate. The ethylacetate solution was washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography (Zorbax PRO 18, acetonitrile/water 60/40) to afford the title compound as a white solid, m.p.65-68 ^{0}C (0.13 g, 8%): ^{1}H-NMR (DMSO-d_6) δ

1.26 (t, J = 6.9 Hz, 3H), 2.51 (s, 3H), 2.64 (t, J = 7.1Hz, 2H), 2.74 (dd, J = 15.4,.9.4 Hz, 1H), 3.06 (dd, J = 15.5, 3.4 Hz, 1H), 3.28 (m, 2H), 3.69 (s, 3H), 3.94 (q, J = 6.9 Hz, 2H), 4.38 (dd, J = 9.2, 3.5 Hz, 1H), 4.98 (s, 2H), 6.50 (s, 1H), 6.82 (m, 5H), 7.36 (m, 10H), 7.54 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.85 (s, 1H), 8.16 (t, J = 5.5 Hz, 1H); MS (FI POS) m/z 639 (M+H); Anal. Calc. for $C_{37}H_{38}N_2O_6S$ C: 69.57, H: 6.00, N; 3.77, found. C: 68.10, H: 5.83, N: 3.77.

Example 77

Preparation of 2-{(2S*, 5S*)-3-(3-acetylphenyl)-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl}-N-[2-(3-ethoxy-4-methoxyphenyl]ethyl]acetamide.

From the HPLC chromatography of the above example, a second compound which was the title compound was obtained as a white solid (0.19 g, 11 %).: m.p. 65-70; Anal. Calc. for $C_{37}H_{38}N_2O_6S$ C: 69.57, H: 6.00, N: 4.39, found C: 69.06, H: 5.96, N: 3.96; ^{1}H-NMR (DMSO-d_6) δ 1.29 (t, J = 6.9 Hz, 3H), 2.51 (s, 3H), 2.66 (t, J = 6.9 Hz, 2H), 2.74 (dd, J = 16.1, 6.4, 1H), 2.96 (dd, J = 16.3, 3.7 Hz, 1H), 3.30 (m, 2H), 3.70 (s, 3H), 4.00 (q, J = 6.9 Hz, 2H), 4.51 (dd, J = 4.1, 4.1, 1H), 5.01 (s, 2H), 6.82 (m, 5H), 7.38 (m, 8H), 7.57 (d, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 1H), 7.89 (s, 1H), 8.15 (t, J = 5.3 Hz, 1H), MS (FI POS) m/z 639 (M+H).

Example 78

Preparation of 2-{(2S*,5R*)-3-(3-benzoylphenyl)-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl}-N-[2-(3-ethoxy-4-methoxyphenyl]ethyl]acetamide.

Using the procedure from the previous two examples, 3-aminobenzophenone (25 g, 127 mmol), 4-benzyloxybenzaldehyde (26.9 g, 127mmol), and mercaptosuccinic acid (57.5 g, 381 mmol) were reacted to obtain [3-(3-benzoylphenyl)-2-(4-benzyloxyphenyl)-4-oxo-1,3-thiazolidin-5-yl]acetic acid (52 g, 78 %).

Using the procedure from the previous two examples a solution of this acid (0.53 g, 1 mmol), 3-ethoxy-4-methoxyphenylethylamine (0.2 g, 1.5 mmol), diisopropylethylamine (0.15 g, 1.2 mmol), and O-(7-azabenzotriazol-1-yl)-N,N,N,N-tetramethyluronium hexafluorophosphate (0.4 g, 1 mmol) in dimethylformamide (20 ml) was reacted to obtain the title compound as a white solid: m.p.70-72 ^{0}C (0.09 g, 13 %): Anal. Calc. for $C_{42}H_{40}N_2O_6S$ C: 71.98, H: 5.75, N: 4.00, found: C: 72.34, H: 5.47, N: 3.77. ^{1}H-NMR (DMSO-d_6) δ 1.26 (t, J = 6.9 Hz, 3H), 2.64 (t, J = 7.1 Hz, 2H), 2.73 (dd, J =

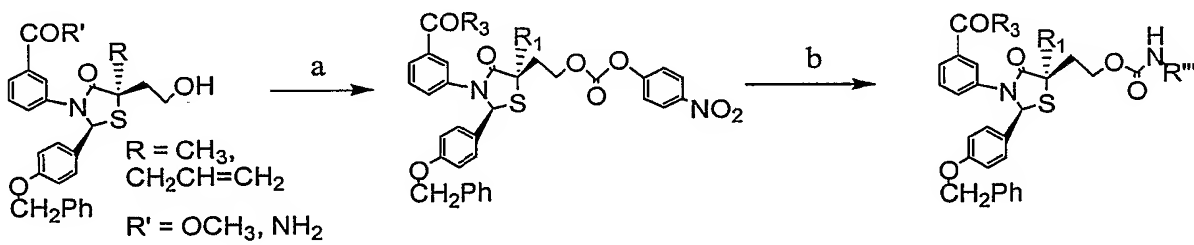
15.5, 9.5 Hz, 1H), 3.05 (dd, J = 15.5, 3.4, 1H), 3.27 (m, 2H), 3.69 (s, 3H), 3.93 (q, J = 6.9 Hz, 2H), 4.38 (dd, J = 9.2, 3.4 Hz, 1H), 5.02 (s, 2H), 6.47 (s, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.76 (s, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 8.7 Hz, 2H), 7.37 (m, 7H), 7.58 (m, 8H), 7.69 (t, J = 7.2 Hz, 1H), 8.14 (t, J = 5.6 Hz, 1H), MS (FI POS) m/z 701 (M+H).

Example 79

Preparation of 2-{(2S*,5S*)-3-(3-benzoylphenyl)-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl}-N-[2-(3-ethoxy-4-methoxyphenyl]ethyl]acetamide.

From the HPLC chromatography of the above example, a second compound which was the title compound was obtained as a white solid (0.25 g, 36 %): m.p. 70-72; Anal. Calc. for $C_{42}H_{40}N_2O_6S$ C: 71.98, H: 5.75. N: 4.00, f. C: 71.93, H: 5.60, N: 3.78. ^{1}H-NMR (DMSO-d_6) δ 1.29 (t, J = 6.9 Hz, 3H), 2.64 (t, J = 7.2 Hz, 2H), 2.70 (dd, J = 5.8, 8.8 Hz, 1H), 2.91 (dd, J = 15.9, 4.0, 1H), 3.27 (q, J = 7.0 Hz, 2H), 3.70 (s, 3H), 3.98 (q, J = 6.9 Hz, 2H), 4.48 (dd, J = 8.5, 3.8 Hz, 1H), 5.04 (s, 2H), 6.39 (s, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.79 (s, 1H), 6.84 (d, J = 8.0, 1H), 6.94 (d, J = 6.8, 2H), 7.36 (m, 7H), 7.58 (m, 8H), 7.68 (t, J = 7.3 Hz, 1H), 8.10 (t, J = 5.6 Hz).

Scheme 6. For Examples 80-91.



a) 4-nitrophenyl chloroformate, pyridine, CH_2Cl_2, 0 °C; **b)** R'''NH_2, CH_2Cl_2, 0 °C.

Example 80

Preparation of 2-{(2S*,5R*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 4-nitrophenyl carbonate.

At 0 °C/N_2 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (1.7 g, 3.8 mmol) in CH_2Cl_2 (50 ml)/pyridine (5 ml) was treated with 4-nitrophenyl chloroformate (1.1 g, 5.7 mmol). After stirring at rt/N_2 for 1.5 hours, it was diluted with water (100 ml) and extracted with CH_2Cl_2 (4x 50 ml). The combined CH_2Cl_2 solution was washed with water, dried with $MgSO_4$ and evaporated. Chromatography of the crude product on silica gel and elution

with 2 % methanol in CH_2Cl_2 afforded 1.9 g (83 % yield) of the title compound as a white solid; ^{1}HNMR (DMSO-d_6): δ 8.40-6.80 (m, 17H, aromatic), 6.61 (s, 1H) 4.99 (s, 2H), 4.59 (m, 2H), 2.62, 2.20 (mm, 2H), 1.69 (s, 3H); MS (ES-positive): $[M+H]^+$ 628; Anal. Calc. For $C_{33}H_{29}N_3O_8S$: C,63.15. H,4.66. N,6.69. Found: C,62.86. H,4.55. N,6.47.

Example 81

Preparation of methyl 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-methyl-5-(2-{[(4-nitrophenoxy)carbonyl]oxy}ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzoate.

Using the procedure of the above example and substituting methyl 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate for 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide the title compound was obtained as a pale white powder: 2.83 g (84% yield). ^{1}HNMR (DMSO-d_6) δ 1.75 (s, 3H), 2.09 (dt, J = 15.04, 3.90 Hz, 1H), 2.61 (m, 1H), 3.62 (s, 3H), 4.51 (m, 2H), 4.99 (s, 2H), 6.69 (s, 1H), 6.84 (d, J = 8.46 Hz, 2H), 7.28 (m, 8H), 7.53 (d, 8.82 Hz, 2H), 7.59 (dt, J = 7.2, 0.75 Hz, 1H), 7.68 (d, J = 7.65 Hz, 1H), 7.98 (s, 1H), 8.32 (d, J = 8.81 Hz, 2H). MS ESI$^+$ 643.

Example 82

Preparation of 2-{(2S*,5R*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 2-(3-ethoxy-4-methoxyphenyl)ethylcarbamate.

At -10 °C/N_2 2-{(2S*,5R*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 4-nitrophenyl carbonate (200 mg, 0.31 mmol) in dichloromethane (10 ml) was treated with 3-ethoxy-4-methoxyphenethyl-amine (200 mg, 1.03 mmol) in CH_2Cl_2 (2 ml). After stirring at 0^0/ N_2 for 5 hours, it was diluted with aqueous 1 N hydrochloric acid (50 ml) and extracted with CH_2Cl_2 (4x50 ml). The CH_2Cl_2 solution was washed with water, dried with $MgSO_4$ and evaporated. Chromatography of the crude product on silica gel and elution with 2 % methanol in CH_2Cl_2 afforded 204 mg (90 % yield) of the title compound as a white solid; ^{1}HNMR (DMSO-d_6): δ 8.0-6.6 (m, 16H), 6.55 (s, 1H) 4.98 (s, 2H), 4.20 (m, 2H), 3.96 (q, 2H), 3.69 (s, 3H), 3.18 (m, 2H), 2.62 (t, 2H), 2.20 (m, 2H), 1.64 (t, 3H), 1.29 (t, 3H); MS (ES-positive): $[M+H]^+$ 684; Anal. Calc. For $C_{38}H_{41}N_3O_7S$: C,66.74. H,6.04. N,6.14. Found: C,66.75. H,6.23. N,6.07.

Example 83

Preparation of 2-[2-(4-benzyloxy-phenyl)-3-(3-carbamoyl-phenyl)-5-methyl-4-oxo-thiazolidin-5-yl]-ethyl ester.

Using the procedure of the above example and substituting 3-phenyl-bezylamine in place of 3-ethoxy-4-methoxyphenethyl-amine, the title compound was obtained as a white solid: ^{1}HNMR (DMSO-d_6) δ 1.67 (s, 3H), 2.13 (m, 2H), 4.18 (m, 4H), 4.99 (s, 2H), 6.56 (s, 1H), 6.82 (d, J = 8.85 Hz, 2H), 7.24 (m, 9H), 7.39 (m, 4H), 7.47 (t, J = 8.07 Hz, 2H), 7.52 (d, J = 6.27 Hz, 1H), 7.60 (m, 3H), 7.74)t, J = 6.07 Hz, 1H), 7.81 (s, 1H), 7.91 (s, 1H). MS ESI$^+$ 672.

Example 84

Preparation of 2S*,5R*-(3-ethoxy-4-methoxybenzyl)-carbamic acid 2-[2-(4-benzyloxy-phenyl)-3-(3-carbamoyl-phenyl)-5-methyl-4-oxo-thiazolidin-5yl]-ethyl ester

At rt/N_2 ethoxy-4-methoxybenzaldehyde (3.6 g, 20 mmol) and methyl hydroxylamine HCl salt (4.0 g, 48 mmol) were dissolved in dry pyridine (15 ml) and stirred for 5 hours. The resulting suspension was filtered and filtrate was evaporated at 40^0 under reduced pressure to give a light brown solid. The solid material was dissolved in methanol (25 ml), diluted with water (25 ml) and was cooled at 0^0 to induce crystallization. The white crystalline material was collected by filtration, rinsed with methanol, and dried in vacuum to give 2.75 g (66% yield) of 3-ethoxy-4-methoxybenzaldehyde methoxyoxime as white powder; ^{1}HNMR (DMSO-d_6) δ 8.11(s, 1H), 6.90-7.30 (m, 3H), 4.00 (q, 2H), 3.85 (s, 3H), 3.78 (s, 3H),1.32 (t, 3H); MS (ES-positive): $[M+ H]^+$ 210. HPLC determined that this compound 99 % purity.

At 0^0/N_2 this compound (2.51 g) was dissolved in THF (15 ml) and treated with 1M diborane in THF (36 ml, 36 mmol). The solution was heated under reflux for 2 hours, then cooled to 0^0, treated with water (10 ml) and 20% KOH aqueous solution (10 ml). The mixture was heated under reflux for 1.5 hours and extracted with CH_2Cl_2 Evaporation of CH_2Cl_2 extract and chromatography of crude product on silica gel afforded 2.1 g (62 % yield) of 3-ethoxy-4-methoxybenzylamine as light brown oil; ^{1}HNMR (DMSO-d_6) δ 6.70-7.00 (m, 3H), 4.28 (s, 2H),3.97 (q, 2H), 3.71 (s, 3H), 1.31 (t, 3H).

Using the procedure of Example 83 and substituting 3-ethoxy-4-methoxybenzylamine, the title compound was obtained as a white solid; ^{1}HNMR (DMSO-d_6) δ 6.70-8.00 (m, 16 H), 6.55 (s, 1H), 4.97 (s, 2H), 4.25 (m, 2H), 4.12 (d, J=7.5

Hz, 2H), 3.90 (q, 2H), 3.69 (s, 3H), 2.25 (m, 2H), 1.64 (s, 3H), 1.26 (t, 3H); MS (ES-positive): $[M+H]^+$ 670. HPLC determined that this compound 90.3 % purity.

Example 85

Preparation of 2-{(2S*,5R*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 2-(3-chlorophenyl)ethylcarbamate

Using the procedure of Example 83 and substituting 3-chlorophenethylamine, the title compound was obtained as a white solid; ^{1}HNMR (DMSO-d_6) δ 6.80-8.00 (m, 17 H), 6.55 (s, 1H), 4.99 (s, 2H), 4.17 (m, 2H), 3.23 (m, 2H), 2.71 (t, 2H), 2.17 (m, 2H); MS (ES-positive): $[M+H]^+$ 644. HPLC determined that this compound 90.8 % purity.

Example 86

Preparation of 2-{(2S*,5R*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 2-(3-trifluoromethoxyphenyl)ethylcarbamate

Using the procedure of Example 83 and substituting 3-triflouromethoxyphenethylamine, the title compound was obtained as a white solid; ^{1}HNMR (DMSO-d_6) δ 6.80-8.00 (m, 17 H), 6.55 (s, 1H), 5.00 (s, 2H), 4.25 (m, 4H), 2.20 (m, 2H), 1.65 (s, 3H); MS (ES-positive): $[M+H]^+$ 680. HPLC determined that this compound 93.9 % purity.

Example 87

Preparation of 2-{(2S*,5R*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 2-(3-trifluoromethylphenyl)ethylcarbamate

Using the procedure of Example 83 and substituting 3-trifluoromethylphenethylamine, the title compound was obtained as a white solid; ^{1}HNMR (DMSO-d_6) δ 6.70-8.00 (m, 17 H), 6.55 (s, 1H), 4.98 (s, 2H), 4.30 (m, 4H), 2.25 (m, 2H), 1.64 (s, 3H); MS (ES-positive): $[M+H]^+$ 664. HPLC determined that this compound 92.1 % purity.

Example 88

Preparation of 2-{(2S*,5R*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 2-(3-iodophenyl)ethylcarbamate

Using the procedure of Example 83 and substituting 3-iodophenethylamine, the title compound was obtained as a white solid; ^{1}HNMR (DMSO-d_6) δ 6.70-8.15 (m, 17 H), 6.55 (s, 1H), 4.98 (s, 2H), 4.17 (m, 4H), 2.25 (m, 2H), 1.65 (s, 3H); MS (ES-positive): $[M+H]^+$ 722; HPLC determined that this compound 91.3 % purity.

Example 89

Preparation of 2-{(2S*,5R*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 4-(1,2,3-thiadiazol-5-yl)benzylcarbamate

Using the procedure of Example 83 and substituting 4-(1,2,3-thiadiazol-5-yl)benzylamine, the title compound was obtained as a white solid; ^{1}HNMR (DMSO-d_6) δ 1.66 (s, 3H), 2.18 (m, 1H), 2.32 (m, 1H), 4.16 (m, 1H), 4.27 (d, J = 6.18 Hz, 2H), 4.28 (m, 1H), 4.96 (s, 2H), 6.57 (s, 1H), 6.82 (d, J = 8.56 Hz, 2H), 7.25 (m, 8H), 7.38 (m, 4H), 7.61 (d, J = 7.65 Hz, 1H), 7.78 (t, J = 6.18 Hz, 1H), 7.81 (s, 1H), 7.96 (s, 1H), 8.20 (d, J = 8.08 Hz, 2H), 9.59 (s, 1H). MS (ESI) M^+ m/z =680.

Example 90

Preparation of 2-{(2S,5R)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 1,3-benzodioxol-5-ylmethylcarbamate

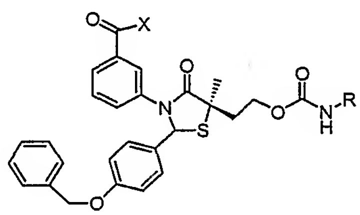
Using the procedure of Example 83 and substituting 1,3-benzodioxol-5-ylmethylamine, the title compound was obtained as a white solid; ^{1}HNMR (DMSO-d_6) δ 1.62 (s, 1H), 2.11 (m, 1H), 2.26 (m, 1H), 4.06 (d, J = 5.65 Hz, 2H), 4.09 (m, 1H), 4.23 (m, 1H), 4.99 (s, 2H), 5.98 (s, 2H), 6.56 (s, 1H), 6.69 (d, J = 8.08 Hz, 1H), 6.79 (d, J = 8.06 Hz, 2H), 6.84 (d, J = 8.53 Hz, 2H),7.26 (m, 8H), 7.40 (m, 2H), 7.61 (d, J = 6.92 Hz, 2H), 7.81 (s, 1H), 7.87 (s, 1H). MS (ESI) M^- m/z = 638.

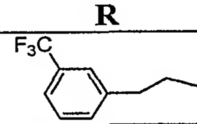
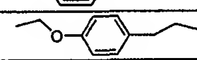
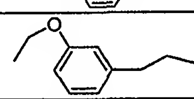
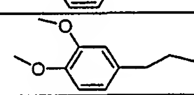
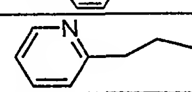
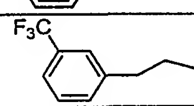
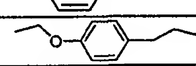
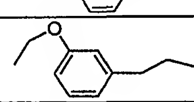
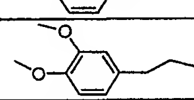
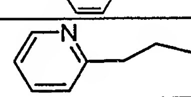
Example 91

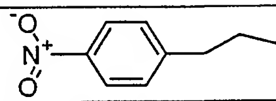
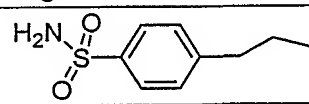
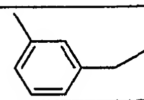
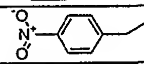
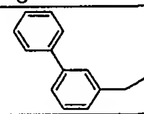
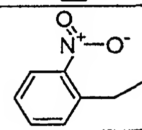
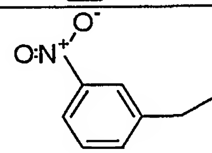
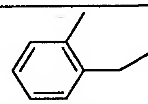
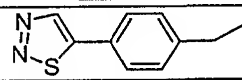
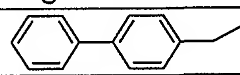
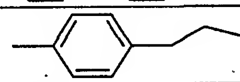
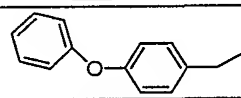
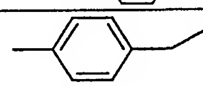
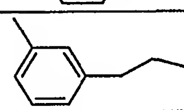
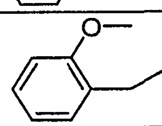
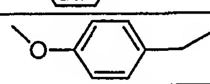
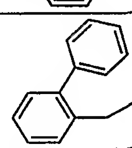
General Procedure for carbamate containing library by parallel synthesis techniques.

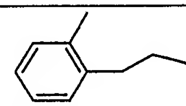
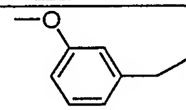
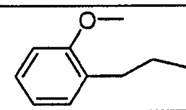
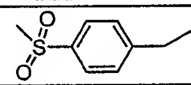
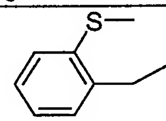
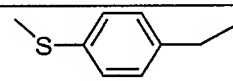
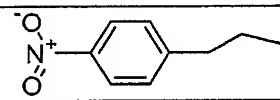
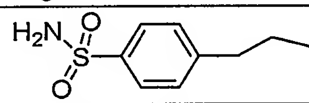
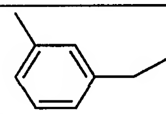
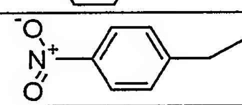
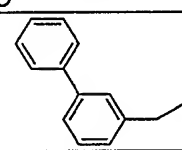
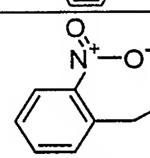
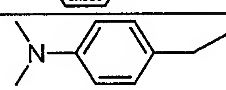
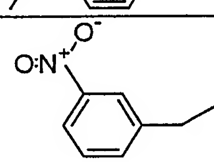
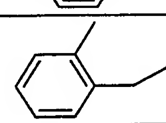
In a vial open to the atmosphere at room temperature, was added carbonate resin (20 mg, 3.18 mmol / g , Argonout Tech. PIN 800 289), the corresponding

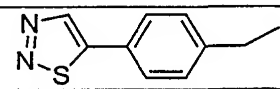
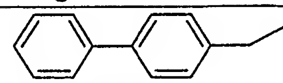
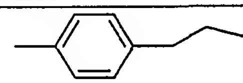
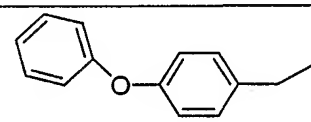
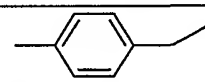
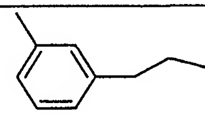
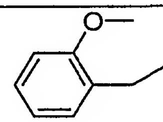
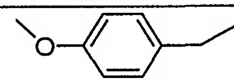
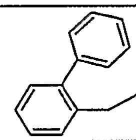
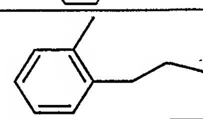
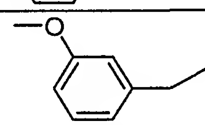
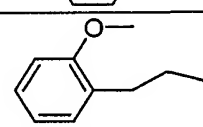
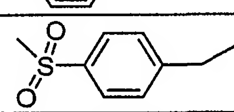
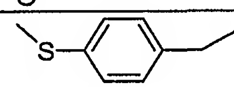
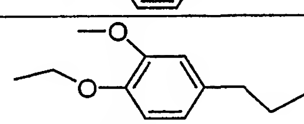
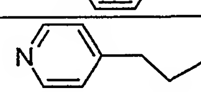
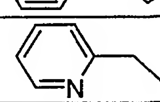
commercially available amine (450 µL, 0.1 M soln in THF), and 2-{(2S*,5R*)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 4-nitrophenyl carbonate or 3-[(2S*,5R*)-2-[4-(benzyloxy)phenyl]-5-methyl-5-(2-{[(4-nitrophenoxy)carbonyl]oxy}ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzoate (300 µL, 0.1 M soln in THF). For each equivalent of hydrochloride contained in each commercial amine employed, an extra amount of carbonate resin was added (20 mg). The resulting yellow mixtures were capped and shaken on an orbital shaker for 5 hrs. To this yellow mixture was added isocyanate resin (20 mg, 1.49 mmol / g, Argonout Tech. PIN 800 262) re-capped and shaken 15 hrs at room temperature. Each yellow mixture was filtered. Each compound was purified by Gilson preparatory HPLC system and the required fractions were collected and concentrated *in vacuuo*. The final products were analyzed by LC / MS.

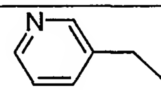
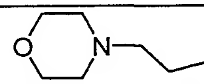
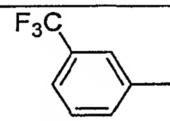
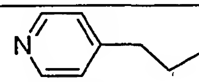
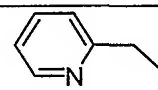
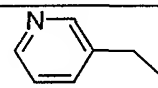
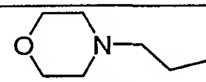
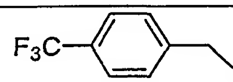
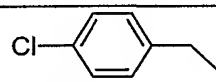
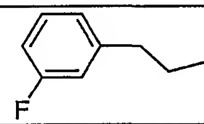
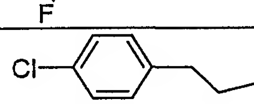
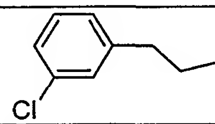
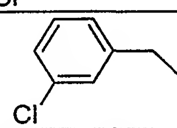
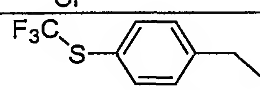
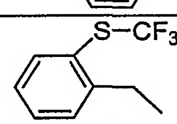
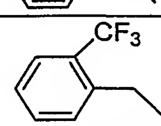
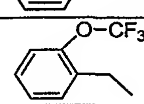


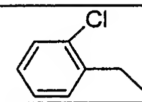
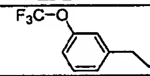
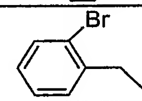
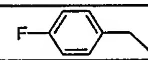
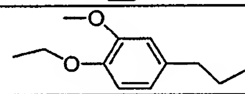
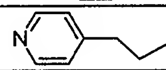
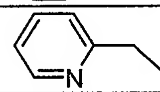
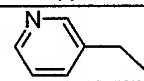
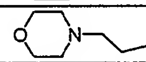
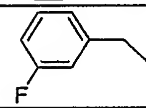
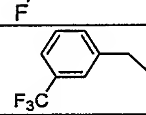
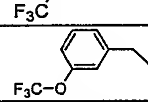
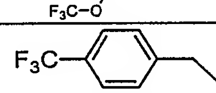
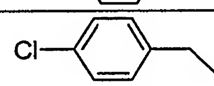
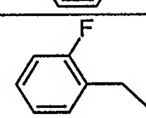
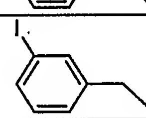
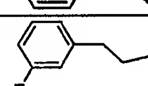
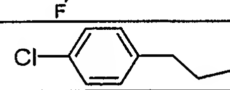
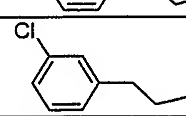
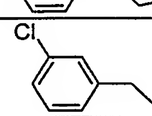
Example 91	X	R	M.S.
A1	OCH_3		694
B1	OCH_3		670
C1	OCH_3		670
D1	OCH_3		686
E1	OCH_3		627
F1	NH_2		679
G1	NH_2		655
H1	NH_2		655
I1	NH_2		671
J1	NH_2		612

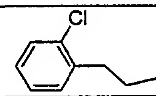
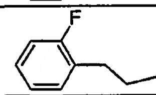
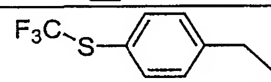
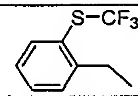
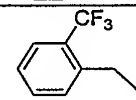
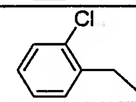
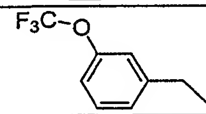
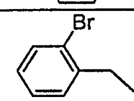
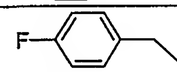
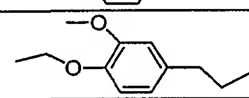
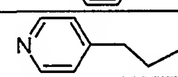
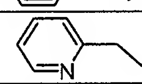
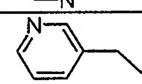
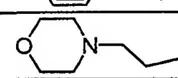
K1	OCH_3		671
L1	OCH_3		705
M1	OCH_3		626
N1	OCH_3		657
O1	OCH_3		688
P1	OCH_3		657
Q1	OCH_3		657
R1	OCH_3		626
S1	OCH_3		696
T1	OCH_3		688
U1	OCH_3		640
V1	OCH_3		704
W1	OCH_3		626
X1	OCH_3		640
Y1	OCH_3		642
Z1	OCH_3		642
A2	OCH_3		688

B2	OCH_3		640
C2	OCH_3		642
D2	OCH_3		656
E2	OCH_3		690
F2	OCH_3		658
G2	OCH_3		658
H2	NH_2		656
I2	NH_2		690
J2	NH_2		611
K2	NH_2		642
L2	NH_2		673
M2	NH_2		642
N2	NH_2		640
O2	NH_2		642
P2	NH_2		611

Q2	NH_2		681
R2	NH_2		673
S2	NH_2		625
T2	NH_2		689
U2	NH_2		611
V2	NH_2		625
W2	NH_2		627
X2	NH_2		627
Y2	NH_2		673
Z2	NH_2		625
A3	NH_2		627
B3	NH_2		641
C3	NH_2		675
D3	NH_2		643
E3	NH_2		684
F3	NH_2		611
G3	NH_2		597

H3	NH_2		597
I3	NH_2		619
J3	OCH_3		699
K3	OCH_3		626
L3	OCH_3		612
M3	OCH_3		612
N3	OCH_3		634
O3	OCH_3		679
P3	OCH_3		645
Q3	OCH_3		643
R3	OCH_3		659
S3	OCH_3		659
U3	OCH_3		645
W3	OCH_3		711
X3	OCH_3		711
Y3	OCH_3		679
Z3	OCH_3		695

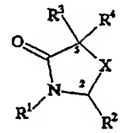
A4	OCH_3		645
B4	OCH_3		695
C4	OCH_3		690
D4	OCH_3		629
E4	OCH_3		699
F4	OCH_3		626
G4	OCH_3		612
H4	OCH_3		612
I4	OCH_3		634
J4	NH_2		614
K4	NH_2		664
L4	NH_2		680
M4	NH_2		664
N4	NH_2		630
O4	NH_2		614
P4	NH_2		722
Q4	NH_2		628
R4	NH_2		644
S4	NH_2		644
T4	NH_2		630

U4	NH_2		644
V4	NH_2		628
W4	NH_2		696
X4	NH_2		696
Y4	NH_2		664
Z4	NH_2		630
A5	NH_2		680
B5	NH_2		675
C5	NH_2		614
D5	NH_2		684
E5	NH_2		611
F5	NH_2		597
G5	NH_2		597
H5	NH_2		619

It is to be understood that the above description is intended to be illustrative and not restrictive. Many embodiments will be apparent to those of skill in the art upon reading the above description. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled. The disclosures of all articles and references, including patent applications and publications, are incorporated herein by reference for all purposes.

WHAT IS CLAIMED:

1. A compound having a formula:



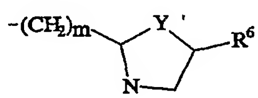
(I)

wherein,

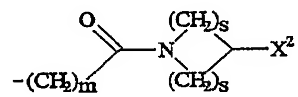
R^1 is a member selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocyclic and substituted heterocylic groups;

R^2 is a member selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocylic groups;

R^3 and R^4 are independently members selected from the group including hydrogen, alkyl, $-(CH_2)_mCONR^5R^6$, $-(CH_2)_mOCONR^5R^6$, $-(CH_2)_mCH_2Y^2R^6$, $-(CH_2)_mCH{=}CHR^6$, $-(CH_2)_mCH_2NR^5CO(Y^3)_nR^6$,



,



R^5 and R^6 are independently members selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, arylalkyl, substituted arylalkyl, heterocyclicalkyl and substituted heterocyclicalkyl groups;

X is a member selected from the group consisting of S, S=O, and O=S=O;

Y is a member selected from the group consisting of O, S, and NH;

Y^2 is a member selected from the group consisting of CH_2, O, S, and NR^5;

Y^3 is a member selected from the group consisting of O, NR^6R^7;

R^7 is a member selected from the group consisting of hydrogen and lower alkyl;

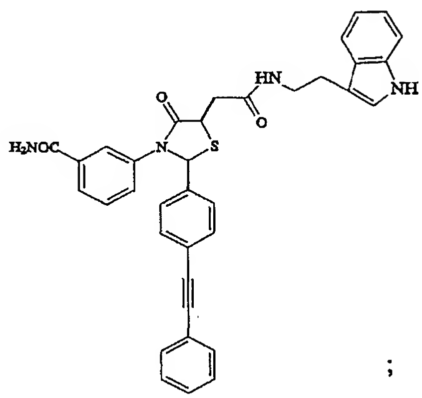
X^2 is a member selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, phenyl, substituted phenyl, heterocyclic, substituted heterocyclic, arylalkyl, substituted arylalkyl, heterocyclicalkyl and substituted heterocyclicalkyl groups;

m is an integer from 0 to 3;

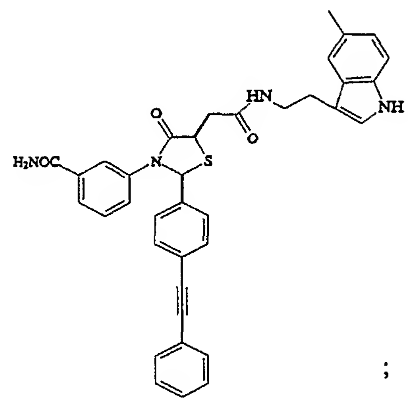
n is 0 or 1; and

s is 1 or 2.

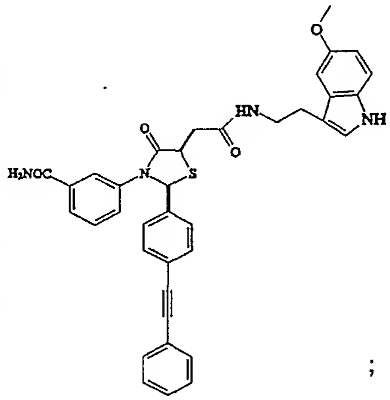
2. A compound according to claim **1**, wherein said compound is a member selected from the group consisting of

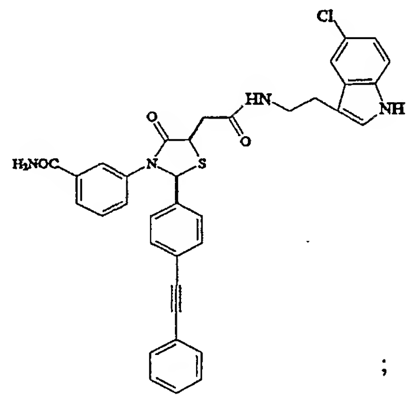


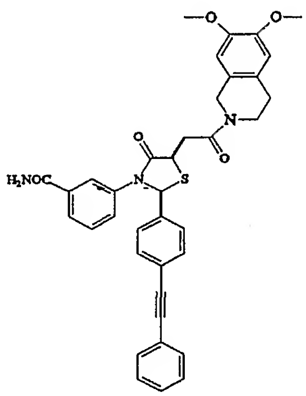
;

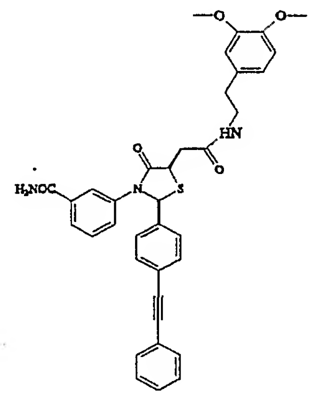


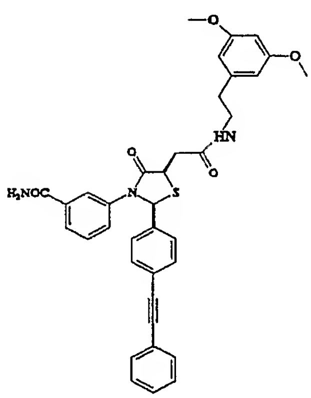
;

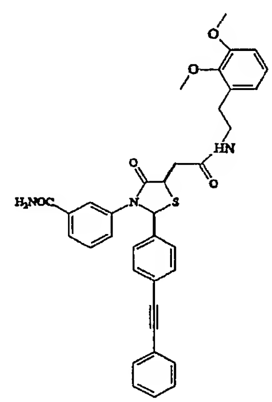

;

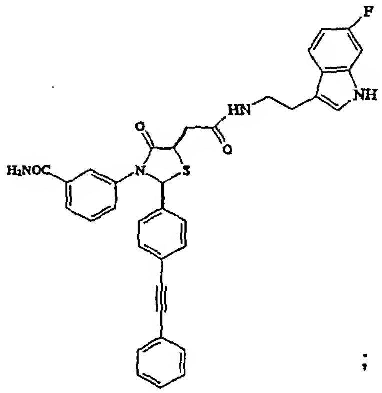

;

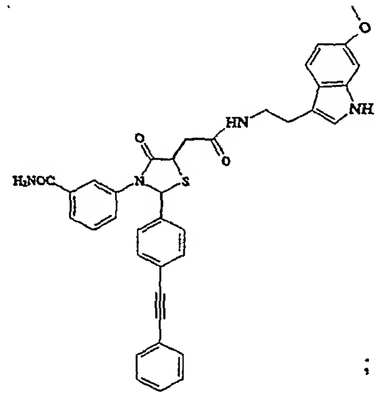

;

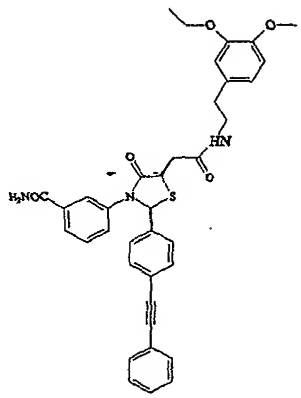

;

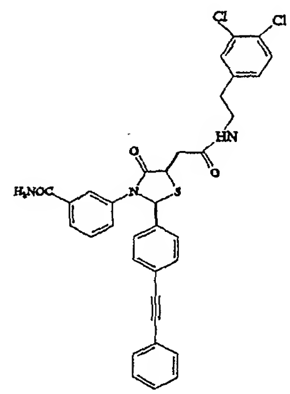

;

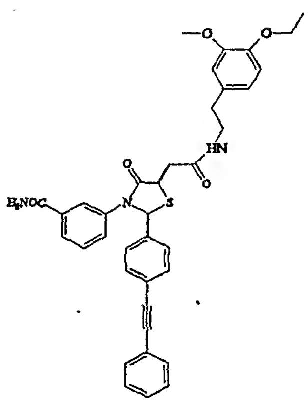

;

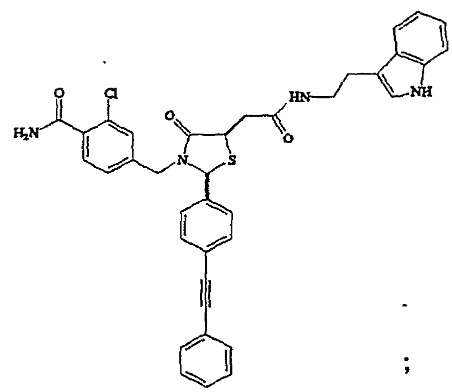

;

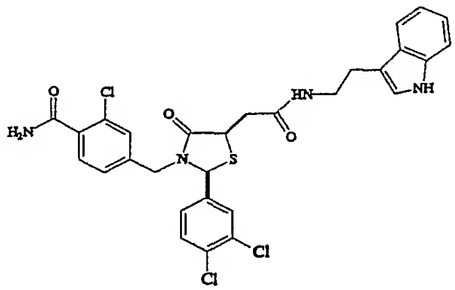

;

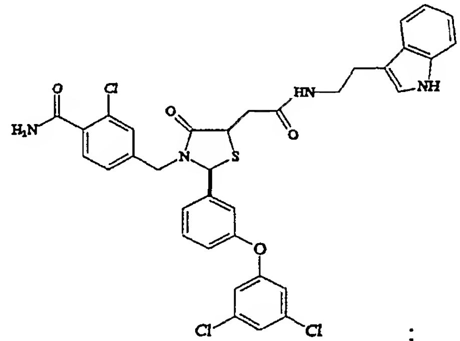

;

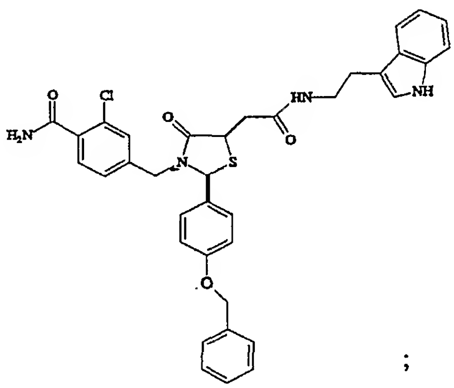

;

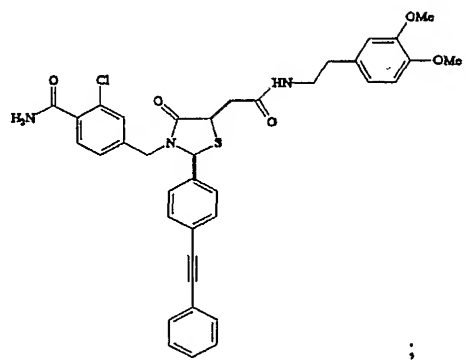

;

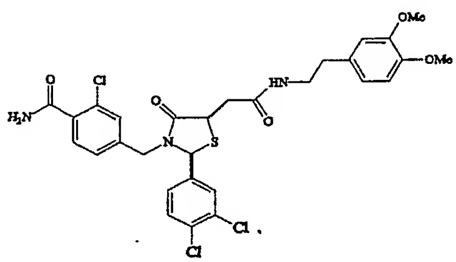

;

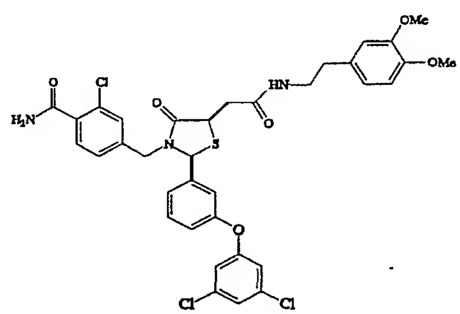

;

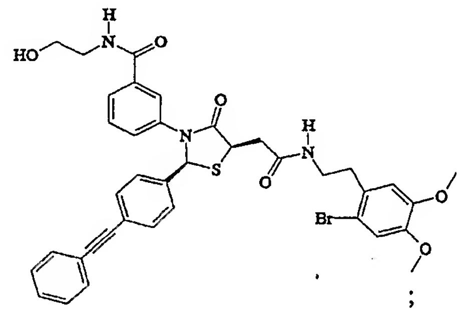

;

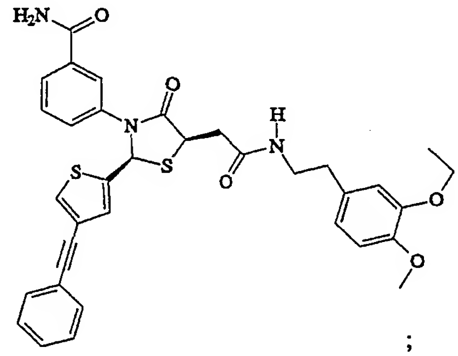

;

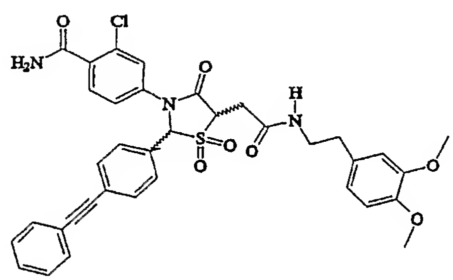

;

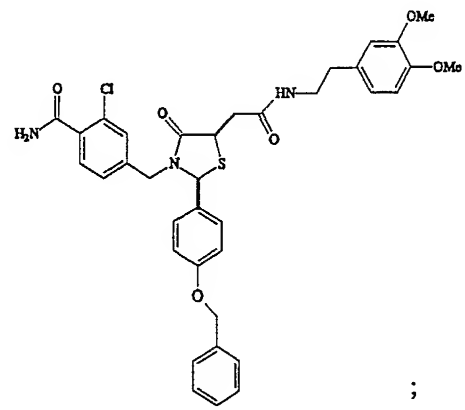

;

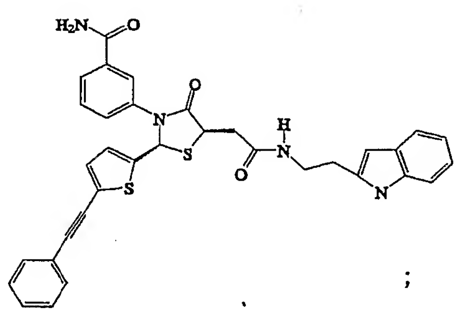

;

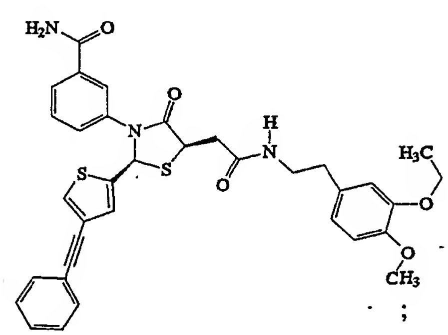

;

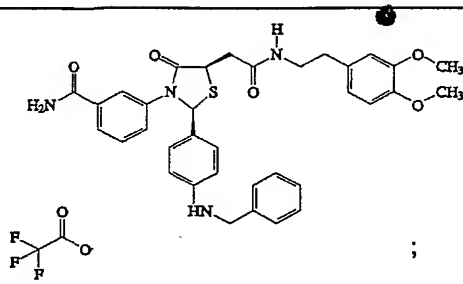

;


;

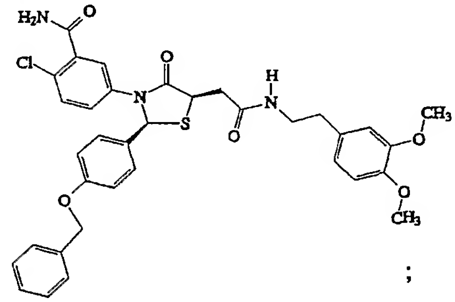

;


;

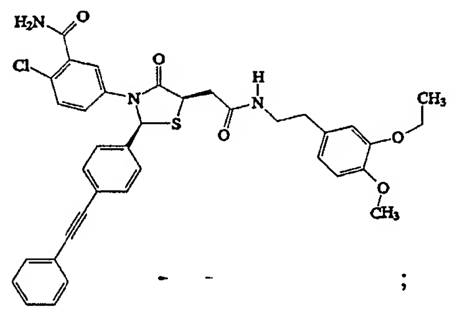

;



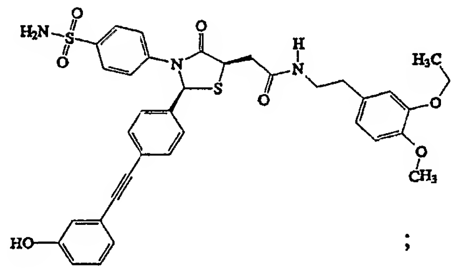
;



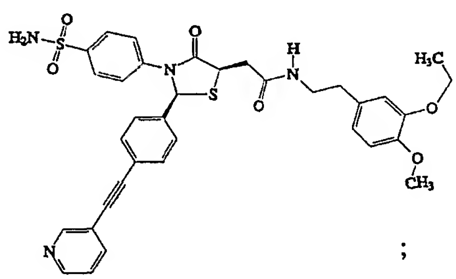
;



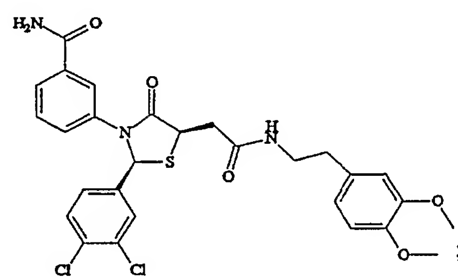
;



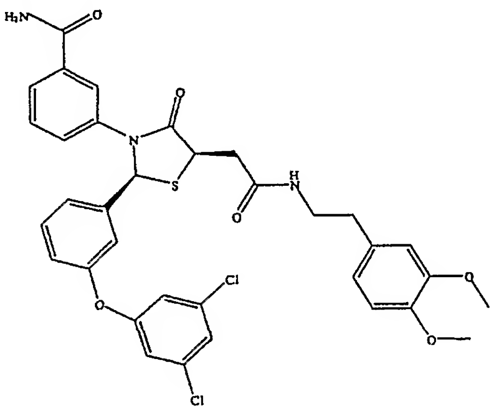
;



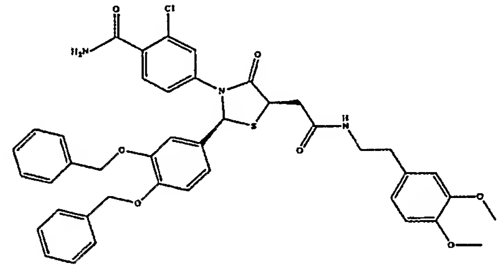
;



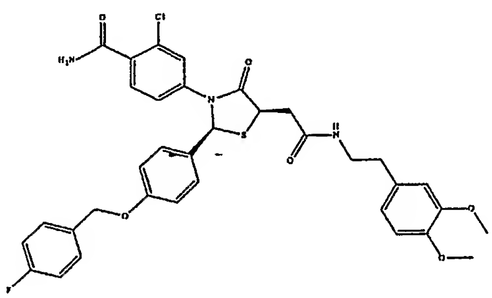
;



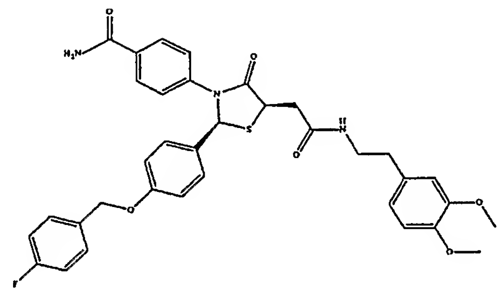
;



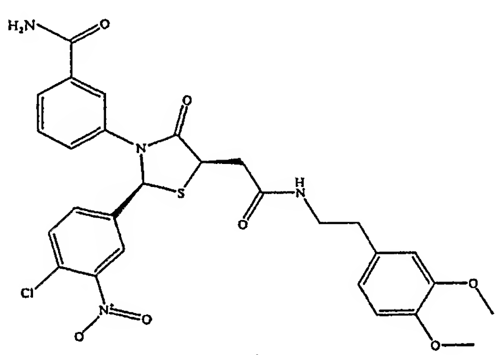
;



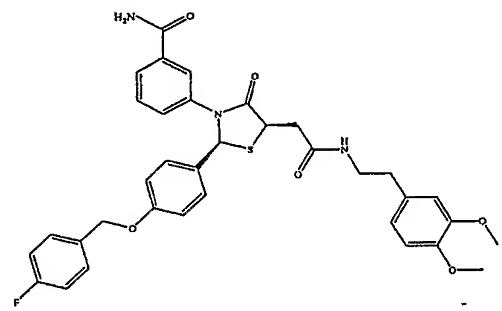
;



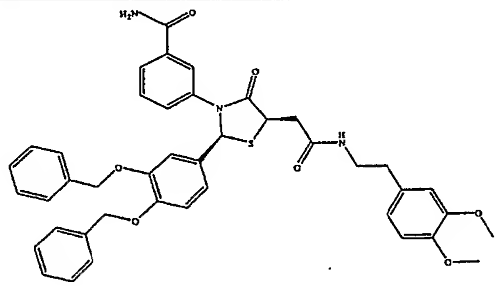
;



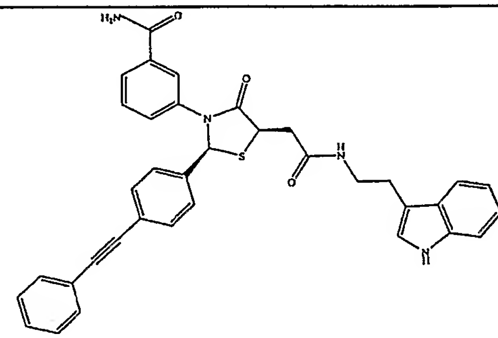
;



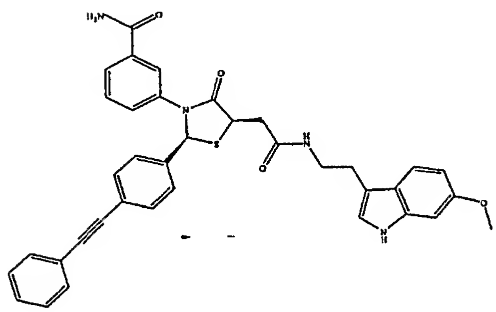
;



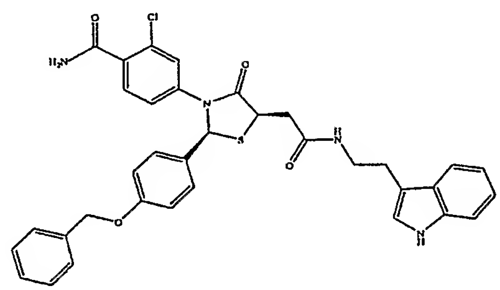
;



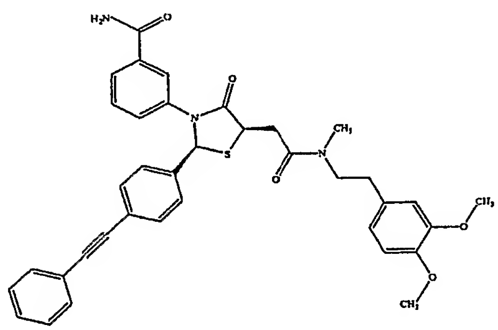
;



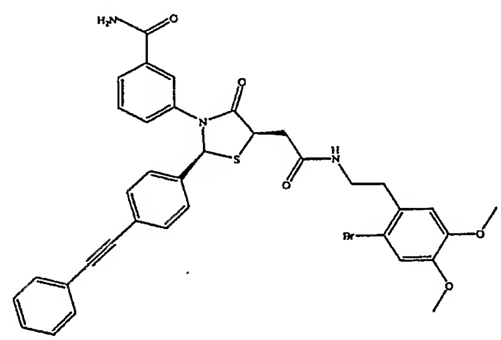
;



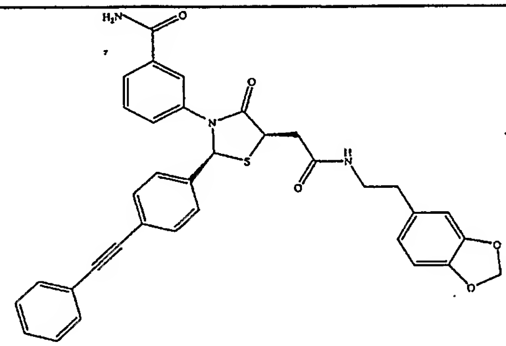
;



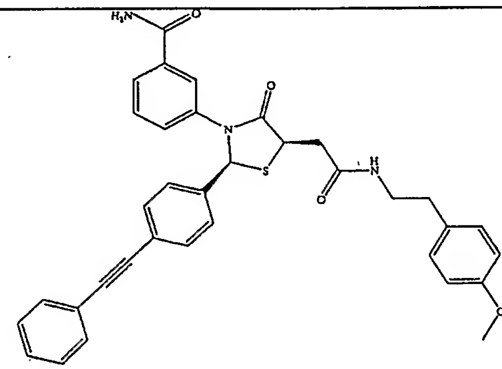
;



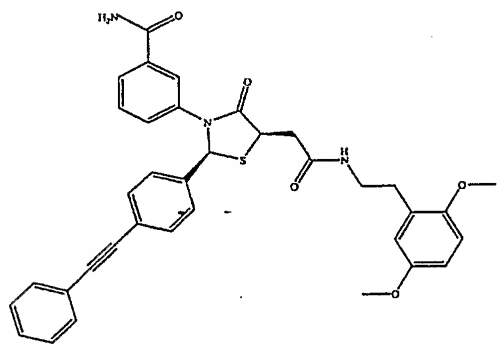
;



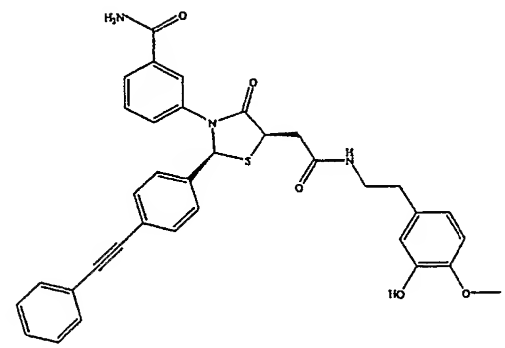
;



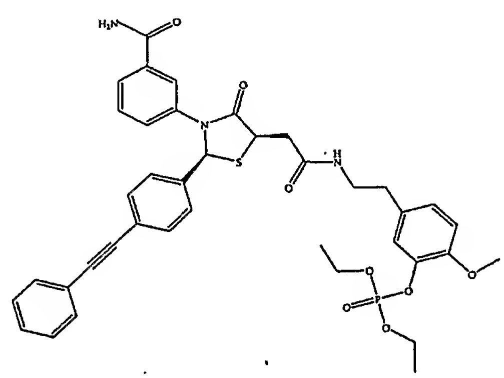
;



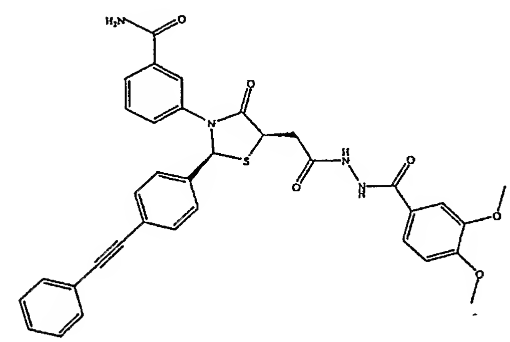
;



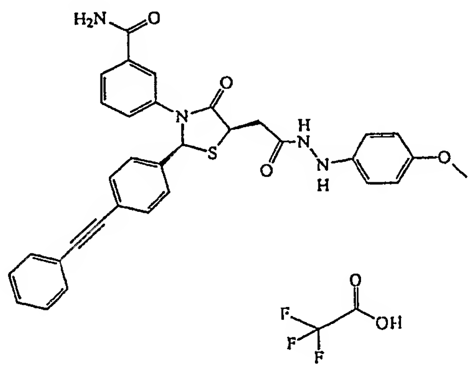
;



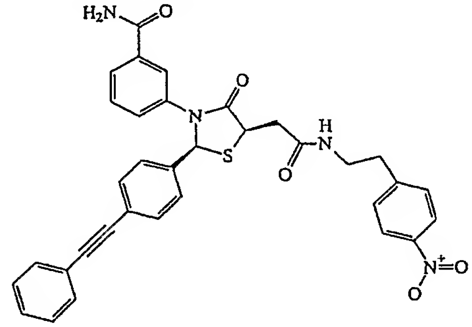
;



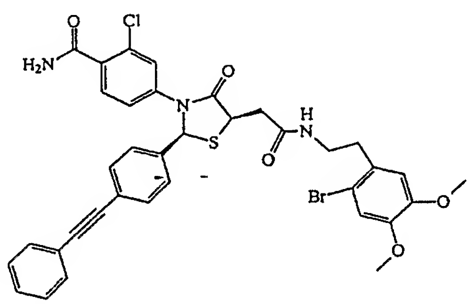
;



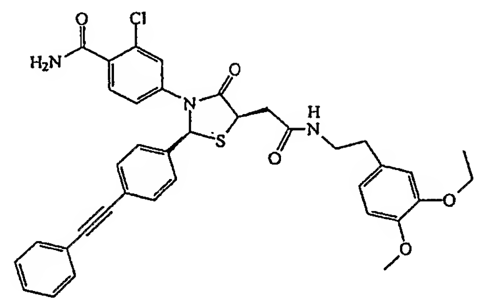
;



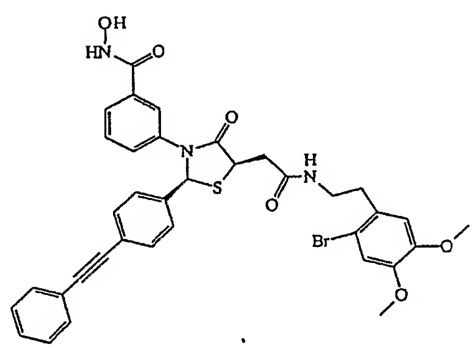
;



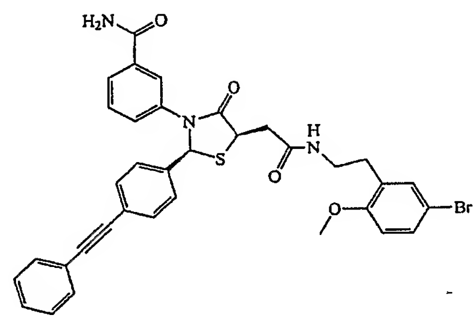
;



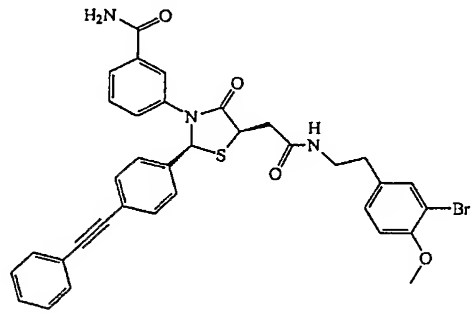
;



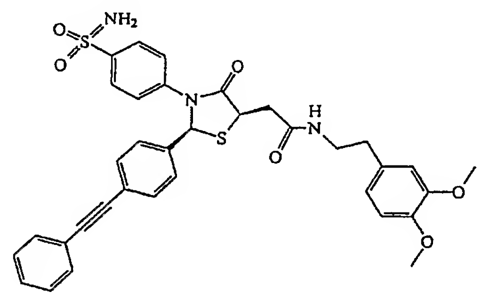
;



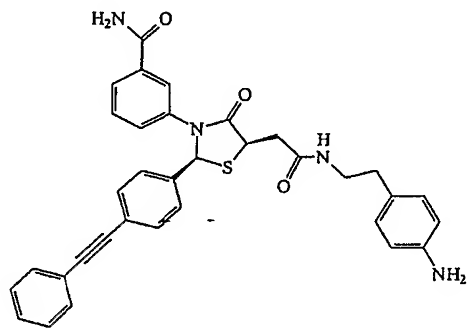
;



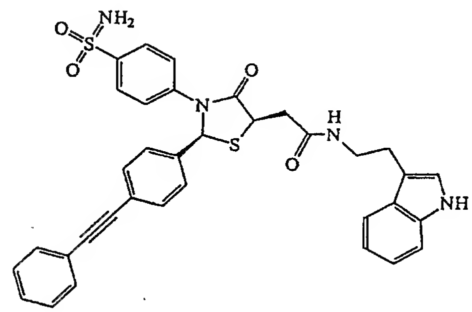
;



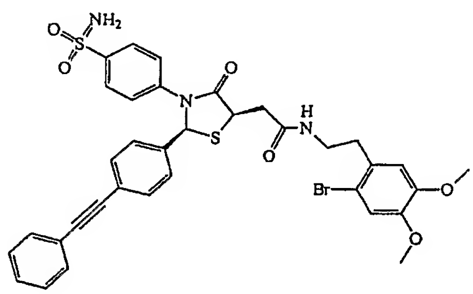
;



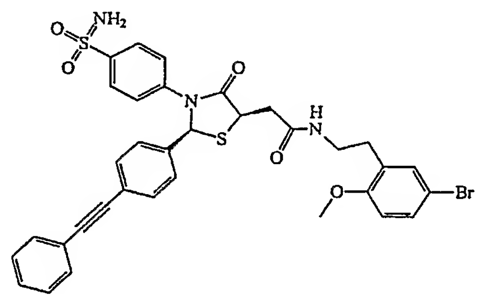
;



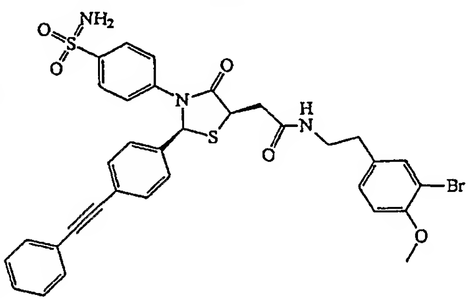
;



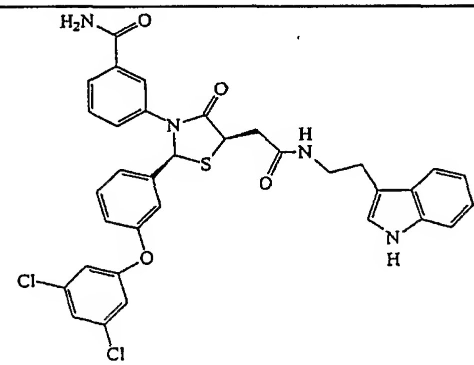
;



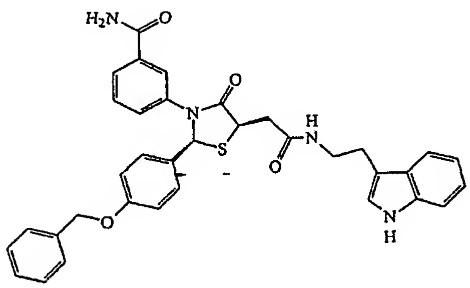
;



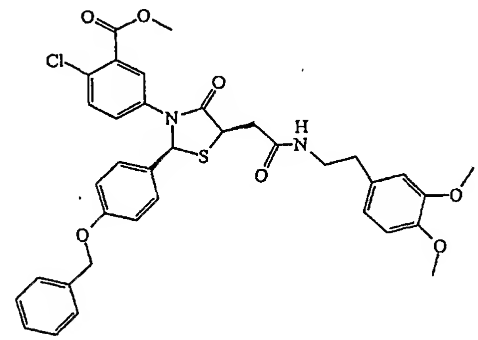
;



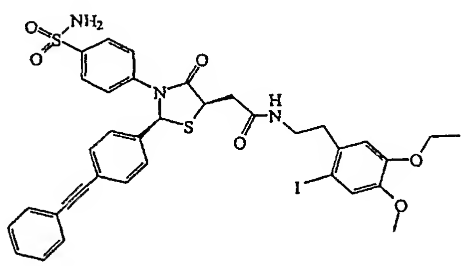
;



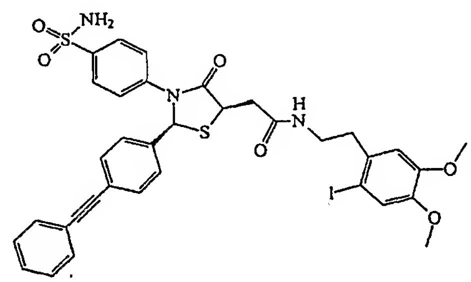
;



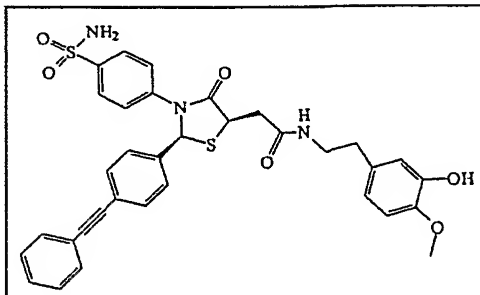
;



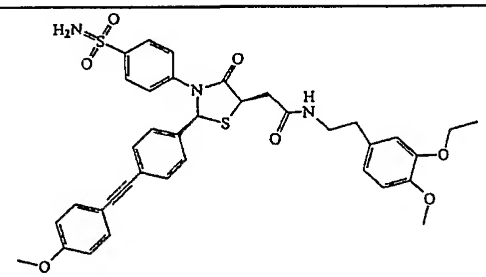
;



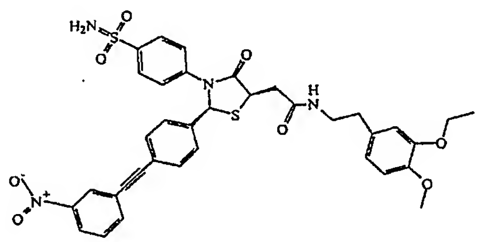
;



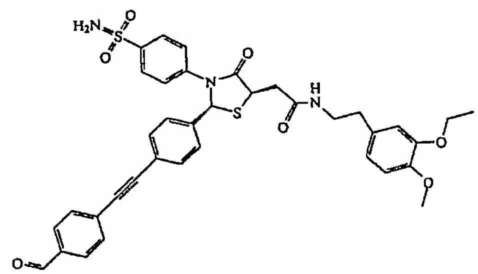
;



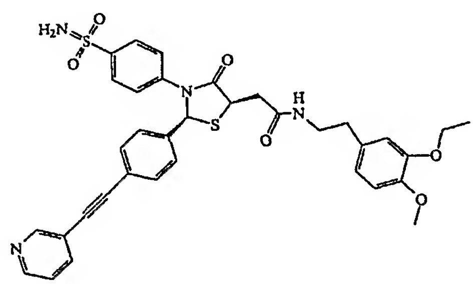
;



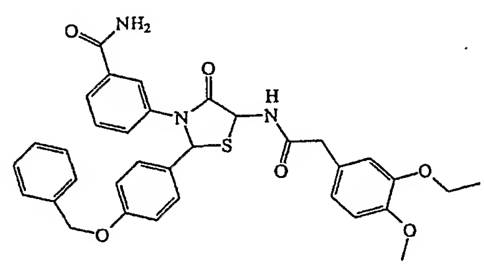
;



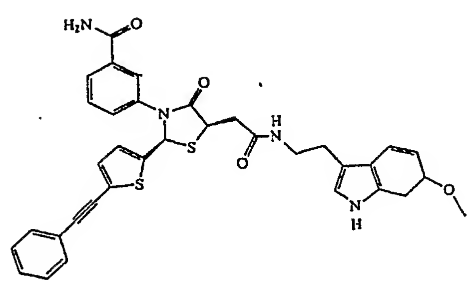
;



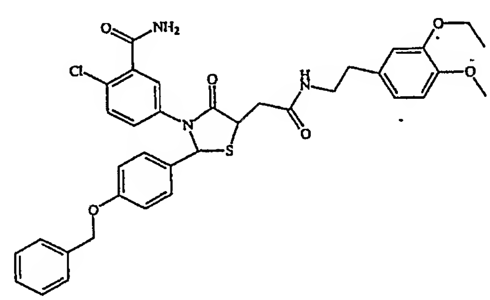
;



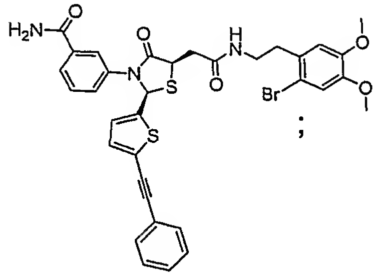
;



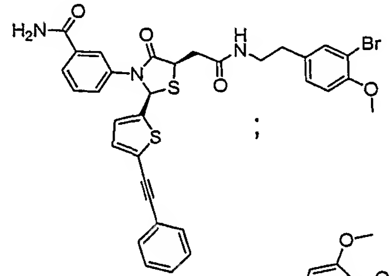
;



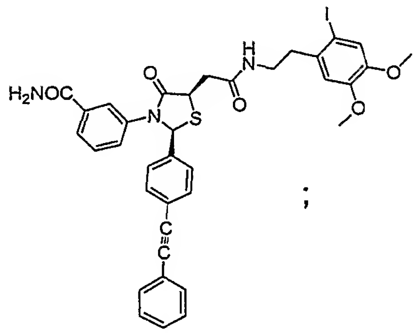
;



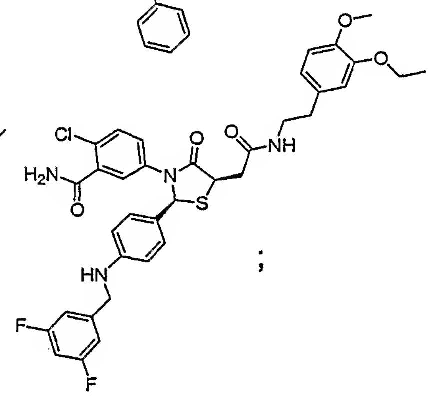
;



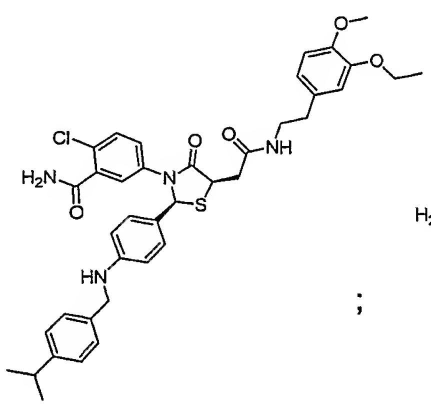
;



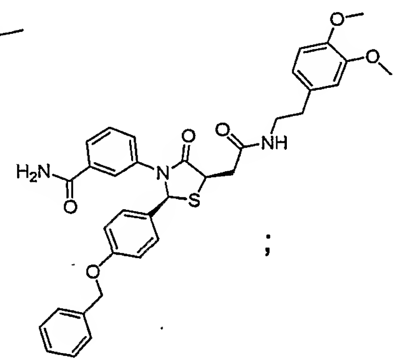
;



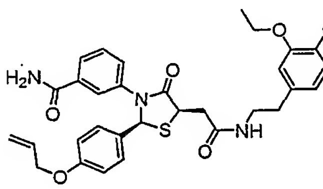
;

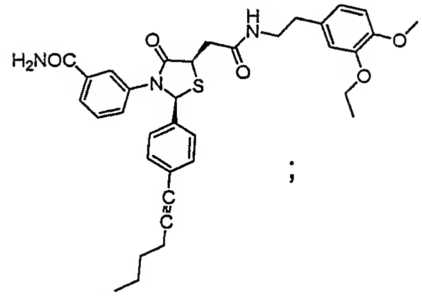


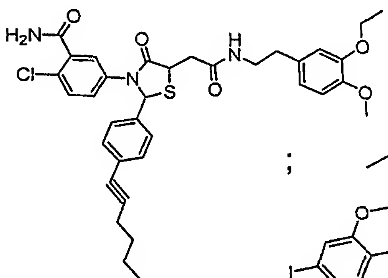
;

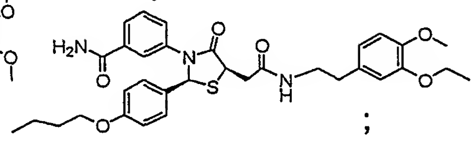


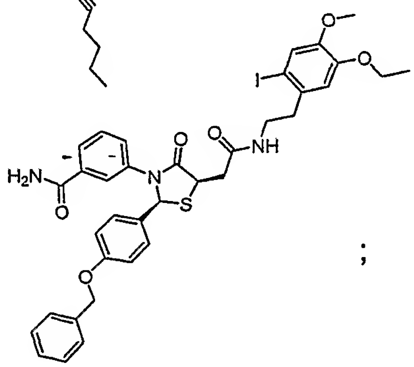
;

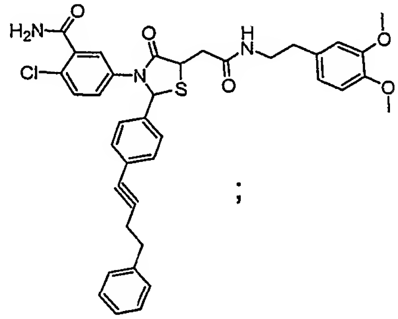

;

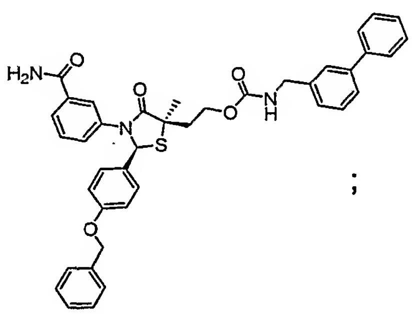

;

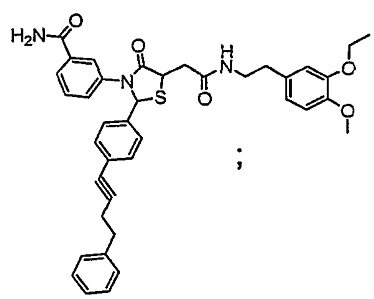

;

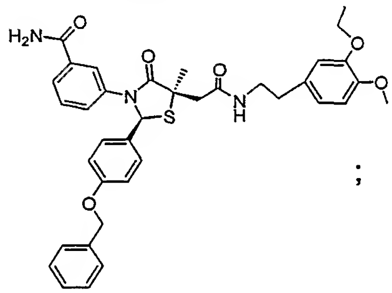

;

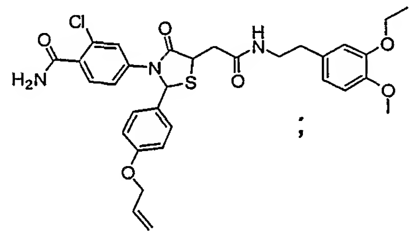

;

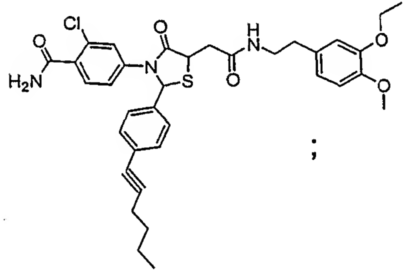

;

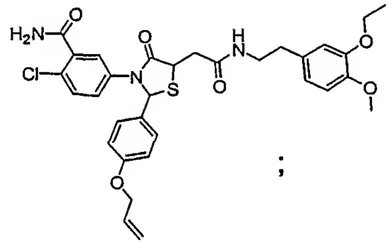

;

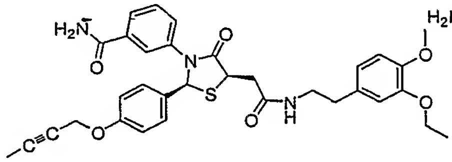

;

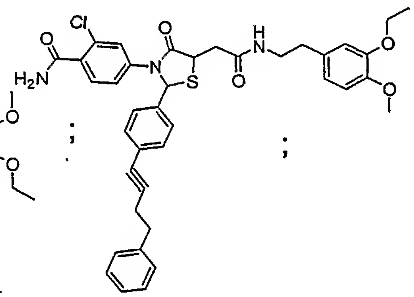

;

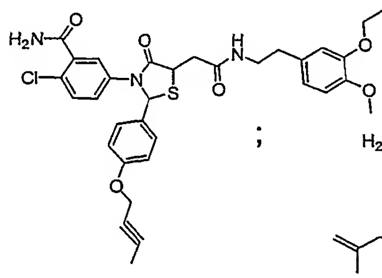

;

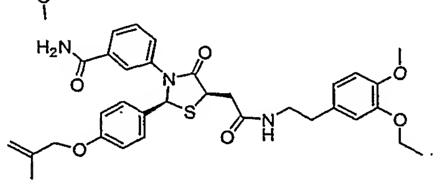

;

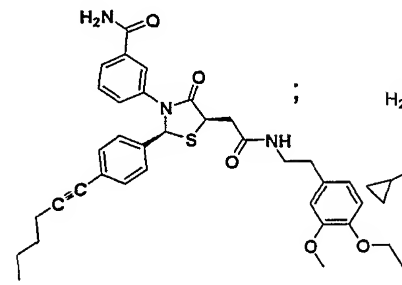
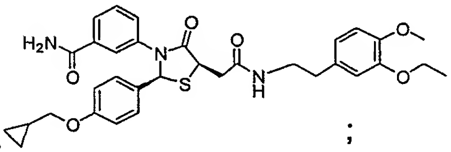
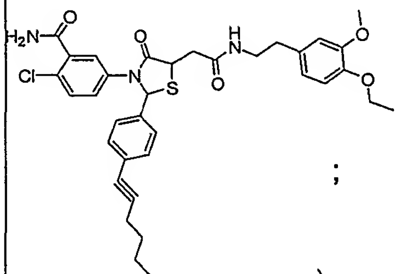
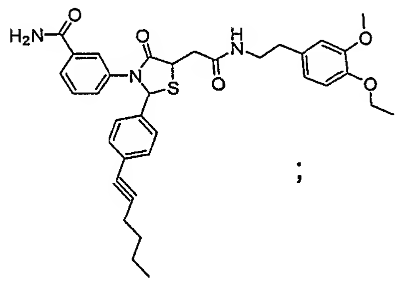
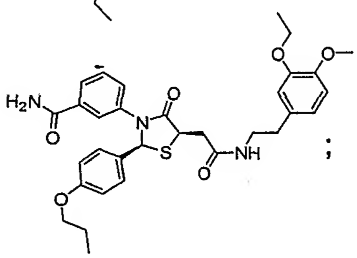
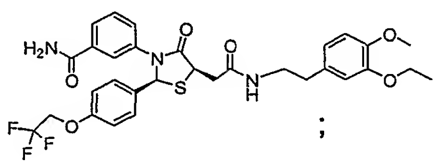
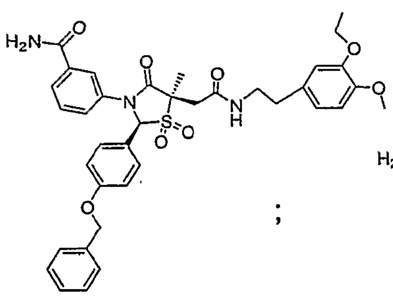
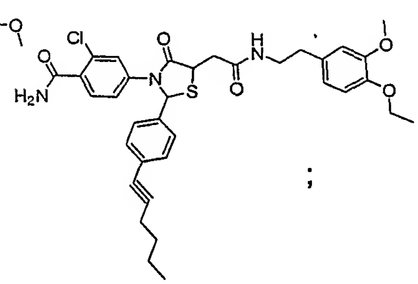

;

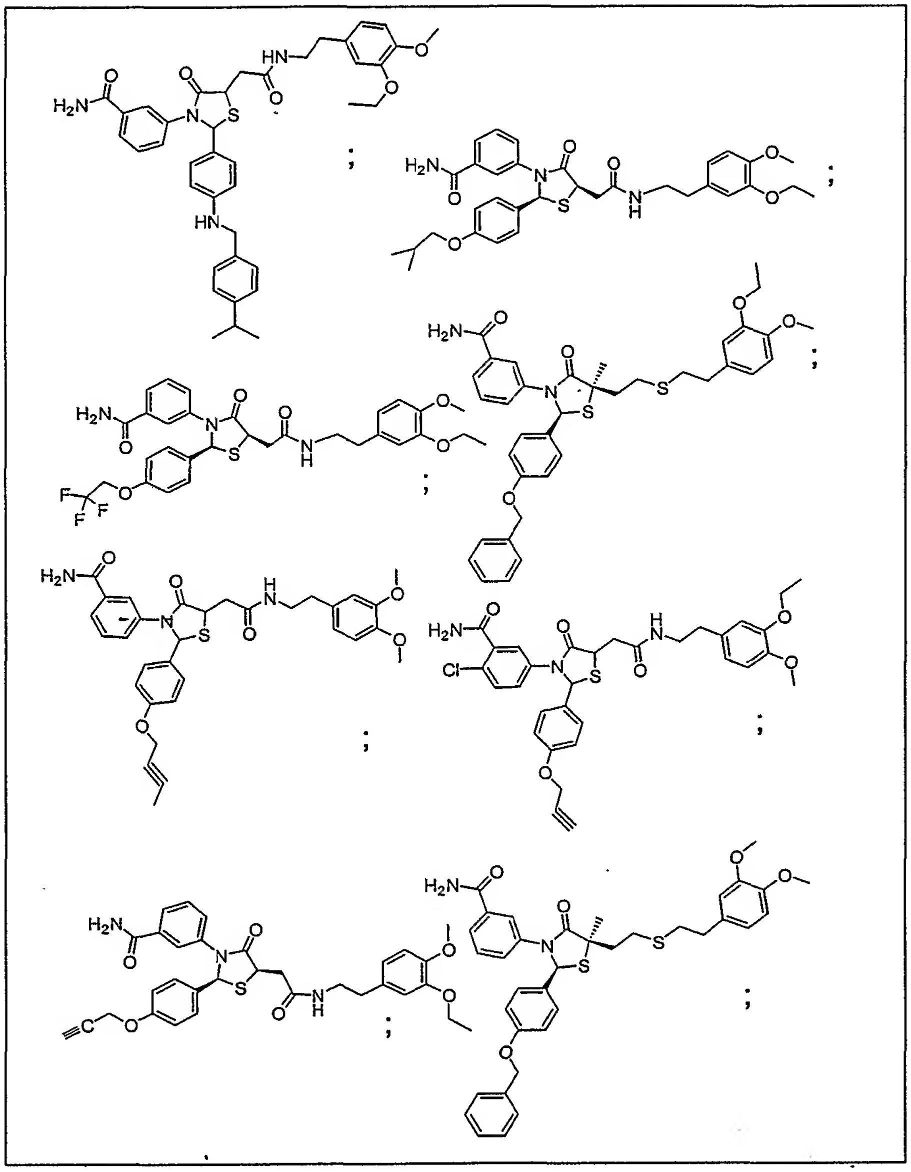

;

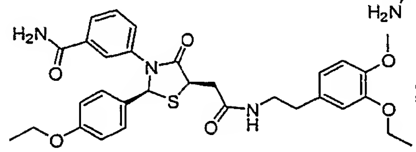

;


;

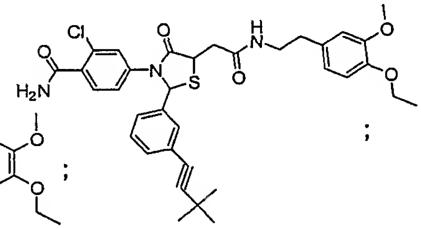

;


;

;

;

;

;

;

;

;

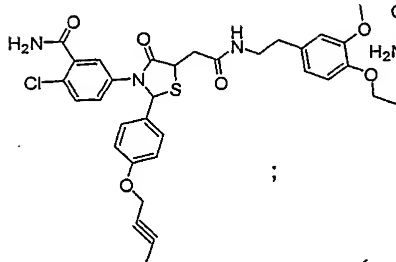




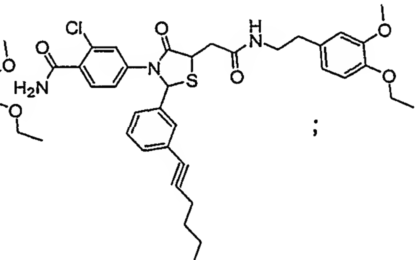
;



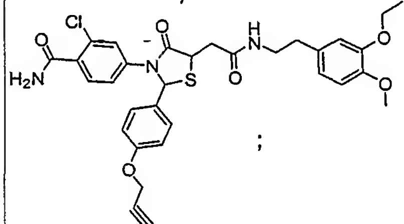
;



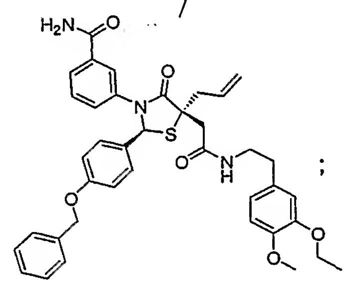
;



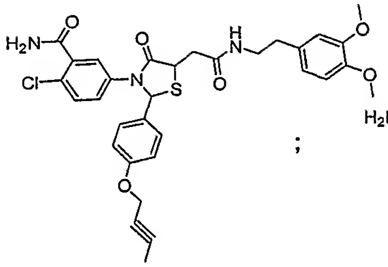
;



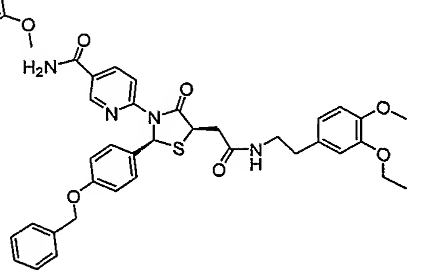
;



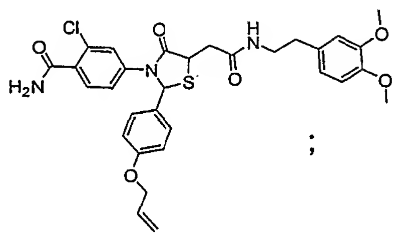
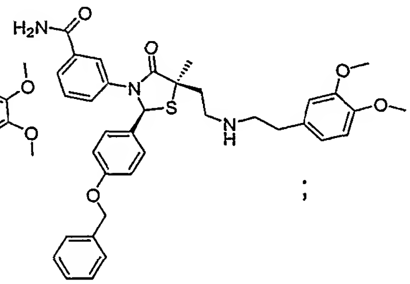
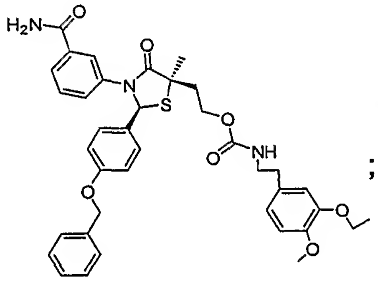
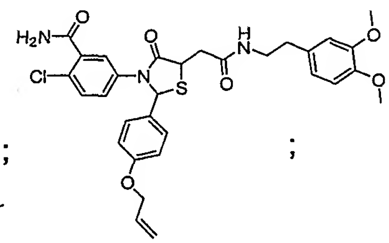
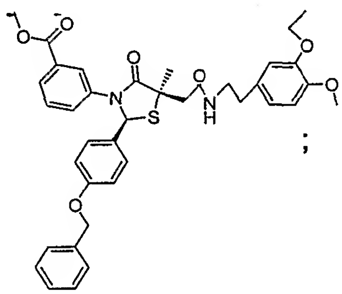
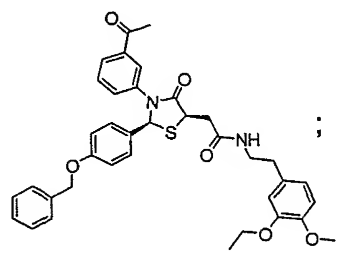
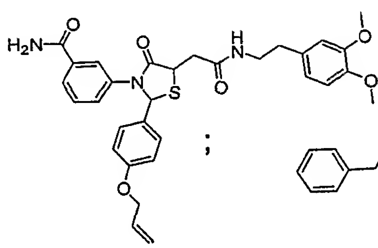
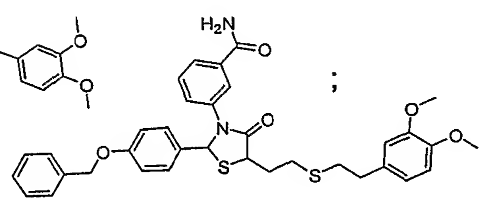
;

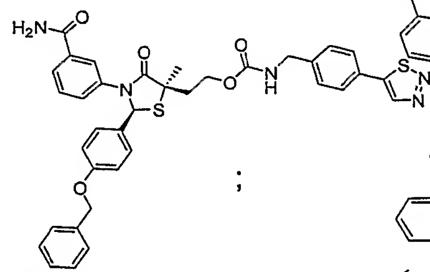


;

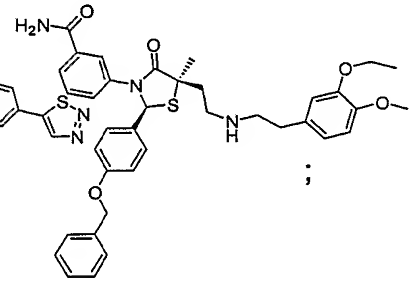


;

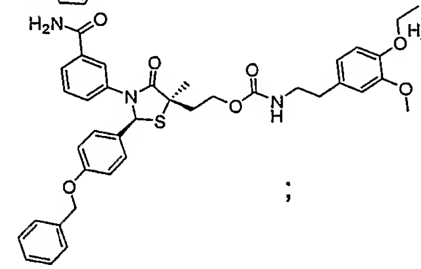

;

;

;

;

;

;

;

;



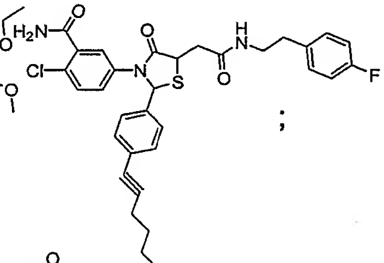
;



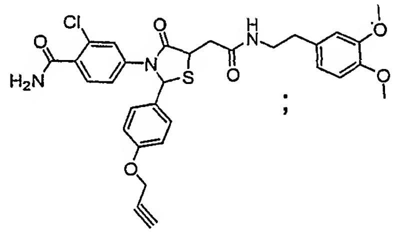
;



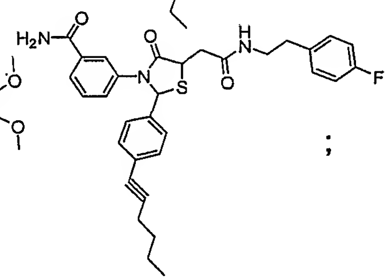
;



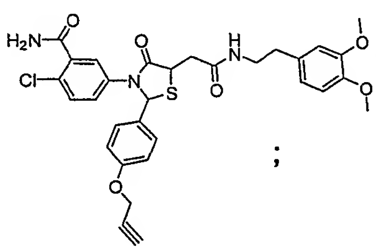
;



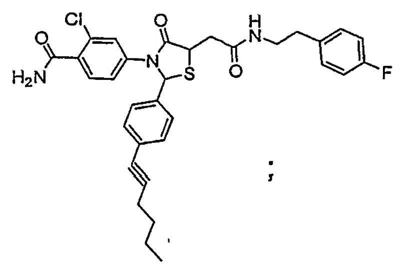
;



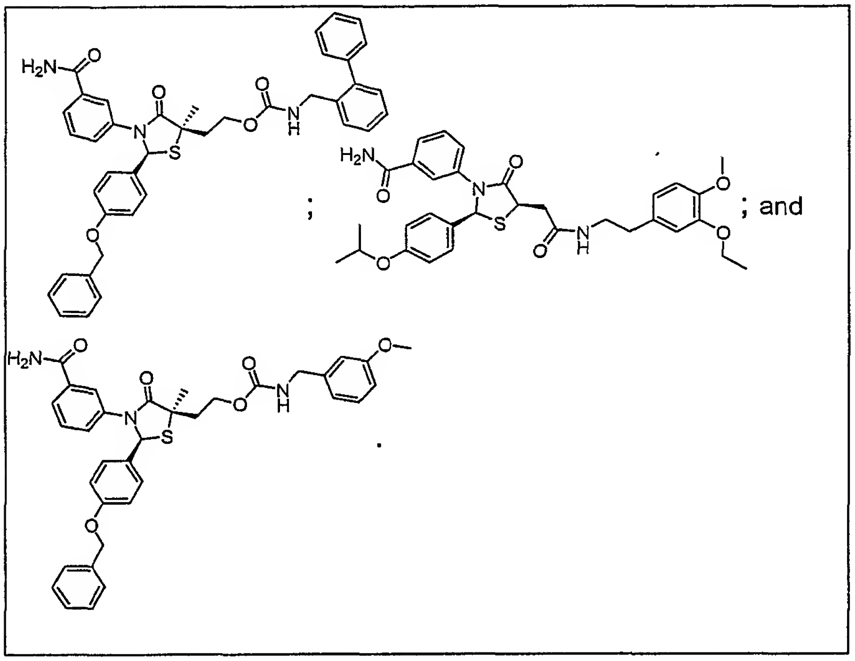
;



;



;



3. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable excipient.

4. A method of activating a FSH receptor comprising contacting a cell comprising the FSH receptor with an effective amount of a compound according to claim 1.

5. A method of stimulating follicle maturation comprising contacting a follicle cell comprising a FSH receptor with an effective amount of a compound according to claim 1.

6. A method for inducing ovulation in a subject comprising administering to said subject an effective amount of a compound according to claim 1.

7. A method for *in vitro* fertilization comprising:

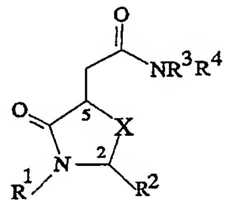
(a) treating a subject with a pharmaceutical formulation according to claim 3;

(b) collecting ova from said subject;

(c) fertilizing said ova; and

(d) implanting said fertilized ova into a host subject.

8. A compound having a formula:



(III)

wherein,

R^1 is a member selected from the group consisting of aryl, substituted aryl, arylalkyl and substituted arylalkyl groups;

R^2 is a member selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic groups;

R^3 and R^4 are independently members selected from the group consisting of hydrogen, alkyl, substituted alkyl, arylalkyl, substituted arylalkyl, heterocyclic and substituted heterocyclic groups; and

X is a member selected from the group consisting of S, S=O, and O=S=O.

9. A FSH receptor agonist, wherein said agonist stimulates the activity of a FSH receptor, wherein said agonist is noncompetitve with FSH for said FSH binding site.

10. An agonist according to claim **9**, wherein said agonist is an organic molecule having a molecular weight of from about 50 daltons to about 1000 daltons.

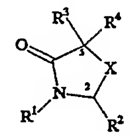
11. A pharmaceutical formulation comprising a non-competitive FSH receptor agonist according to claim **9**.

12. A compound that modulates FSH receptor activity, said compound having:

a molecular weight of from about 200 daltons to about 1000 daltons; and

a FSH modulating activity as expressed by an EC_{50} standard of no more than 200 nM;

wherein said FSH receptor modulating activity of said compound is competitively inhibited by a compound having the formula:



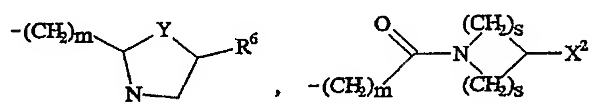
(I)

wherein,

R^1 is a member selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocyclic and substituted heterocylic groups;

R^2 is a member selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocylic groups;

R^3 and R^4 are independently members selected from the group including hydrogen, $-(CH_2)_mCONR^5R^6$, $-(CH_2)_mCH_2Y^2R^6$, $-(CH_2)_mCH{=}CHR^6$, $-(CH_2)_mCH_2NR^5CO(Y^3)_nR^6$,



R^5 and R^6 are independently members selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, arylalkyl, substituted arylalkyl, heterocyclicalkyl and substituted heterocyclicalkyl groups;

X is a member selected from the group consisting of S, S=O, and O=S=O;

Y is a member selected from the group consisting of O, S, and NH;

Y^2 is a member selected from the group consisting of CH_2, O, S, and NR^5;

Y^3 is a member selected from the group consisting of O, and NR^6R^7;

R^7 is a member selected from the group consisting of hydrogen, and lower alkyl;

X^2 is a member selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, phenyl, substituted phenyl, heterocyclic, substituted heterocyclic, arylalkyl, substituted arylalkyl, heterocyclicalkyl and substituted heterocyclicalkyl groups;

m is an integer from 0 to 3;

n is 0 or 1; and

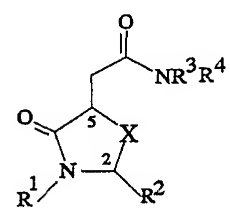
s is 1 or 2.

13. A compound that modulates FSH receptor activity, said compound having:

a molecular weight of from about 200 daltons to about 1000 daltons; and

a FSH modulating activity as expressed by an EC_{50} standard of no more than 200 nM;

wherein said FSH receptor modulating activity of said compound is competitively inhibited by a compound having the formula:



(III)

wherein,

R^1 is a member selected from the group consisting of aryl, substituted aryl, arylalkyl and substituted arylalkyl groups;

R^2 is a member selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic groups; and

R^3 and R^4 are independently members selected from the group consisting of hydrogen, alkyl, substituted alkyl, arylalkyl, substituted arylalkyl, heterocyclic and substituted heterocyclic groups.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/23395

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/427, 433, 4709, 4436, 5377; C07D 277/14, 417/02
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/92, 236.8, 307, 342, 361, 369; 544/133; 546/146, 269.7; 548/119, 127, 131, 137

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN CAS ONLINE, search terms: fsh, cell?, follicl?, ovalat?, fertiliz?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3,328,415 A (SURREY et al.) 27 June 1967 (27.06.67)., see entire document, especially column 1, lines 9-30 and attached compounds of CA Registry Numbers 17972-17-7, 17972-18-8, etc.	1, 3
X	US 5,061,720 A (WALSH et al.) 29 October 1991 (29.10.91), see entire document, especially columns 1-2, and attached compounds of CA Registry Numbers 138618-51-6, 138618-52-7, etc.	1, 3
X	GB 1,409,898 A (CIBA-GEIGY A.G.) 15 October 1975 (15.10.75), see entire document, especially formula 1c on page 4 and attached compounds of CA Registry Numbers 16470-69-2, 43055-98-7, etc.	1, 3

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 OCTOBER 2001	16 NOV 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Joyce Bridgers for LAURA L. STOCKTON Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/23395

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/27832 A2 (GLAXO GROUP LIMITED) 18 May 2000 (18/05/00), see entire document, especially pages 3-4 and attached compounds of CA Registry Numbers 267412-58-8, 267412-59-9, etc.	1, 3, 8
X	Chem. abstr., Volume 87, Number 9, 29 August 1977 (Columbus. OH, USA), page 538, column 2, the abstract No. 68220y, PATEL, D.R. et al. 'Thiazolidinones. Part XIV. Synthesis of 2-aryl-3-aryl-5-alkyl/aryl-4-thiazolidinones.' J. Inst. Chem. (India). 1976, 48, Pt. 6, 305-8 (Eng). See especially attached compounds of CA Registry Numbers 63444-75-7, 63445-27-2, etc.	1, 3

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/92, 236.8, 307, 342, 361, 369; 544/133; 546/146, 269.7; 548/119, 127, 181, 187

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I, claims 1-4 and 8, drawn to products and method.
Group II, claim 5, drawn to a method.
Group III, claim 6, drawn to a method.
Group IV, claim 7, drawn to a method.

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the products of Group I are used in different claimed processes other than the process that is found in Group I. If an application contains claims to more than one of the combinations of categories of invention, unity of invention is not present.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/23395

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 9-13
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

structures of the compounds are not present in the claims (see claims 9 and 12), and therefore, the claims could not be searched.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.